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# ANNALS OF INTERNAL MEDICINE

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NUMBER 1

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## FURTHER OBSERVATIONS ON THE TREATMENT OF TYPHUS FEVER WITH PARA-AMINO- BENZOIC ACID \*

By J. C. SNYDER, M.D., A. YEOMANS, M.D., D. H. CLEMENT, M.D., E. S. MURRAY, M.D., C. J. D. ZARAFONETIS, M.D., and N. A. TIERNEY, M.D.

THE therapeutic effect of para-aminobenzoic acid (PABA) in experimental murine typhus infection of white mice was reported in 1942.<sup>1</sup> Subsequently, evidence bearing on the action of PABA in experimental rickettsial infections has been obtained in several laboratories. In the yolk sac membrane of developing chick embryos, PABA or its sodium salt inhibits the multiplication of *Rickettsia mooseri*,<sup>2, 3</sup> *R. prowazeki*,<sup>2, 4, 5</sup> *R. orientalis*,<sup>5</sup> and *Dermacentroxenus rickettsi*.<sup>4</sup> The mortality in experimental rickettsial infections in white mice,<sup>1, 6</sup> gerbilles,<sup>7, 8, 9</sup> cotton rats,<sup>10</sup> and guinea pigs<sup>11</sup> is considerably reduced by PABA.

In 1944 a favorable therapeutic effect from the administration of PABA to several patients who were in the first week of classical typhus fever was reported from Egypt by Yeomans et al.<sup>12</sup> Successful results in the treatment of 18 cases of tsutsugamushi disease with PABA were obtained by Tierney in Burma.<sup>13</sup> One patient suffering from Rocky Mountain spotted fever was treated by Rose, Duane, and Fischel with apparently beneficial results.<sup>14</sup>

It is the purpose of this paper to record additional experience in the administration of PABA to patients with epidemic louse-borne typhus fever. Part I analyzes statistically the data obtained in 1944<sup>12</sup> from a series of alternate treated and control patients in Cairo, Egypt, together with new data from a similar series of the same size observed in 1945. Part II describes the treatment of 60 patients in an epidemic of typhus in a concentration camp in Germany and of a miscellaneous group of five patients. Part III states several points of importance in the administration of PABA in human rickettsial infections.

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From the United States of America Typhus Commission, War Department, Washington, D. C., and the Laboratories of the International Health Division of The Rockefeller Foundation, New York.

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## PART I

ALTERNATE CONTROL AND PABA-TREATED TYPHUS FEVER PATIENTS,  
CAIRO, EGYPT, 1944-1945

In 1944 it was possible to study a small group of patients who met certain criteria at the time they were admitted to the experimental ward established by the United States of America Typhus Commission in the Cairo Fever Hospital, through the courtesy of Egyptian officials.<sup>15</sup> These patients were placed alternately in control and PABA-treated groups. In 1945 a similar study was carried out in the same ward. Considered together, the cases of the two years can be analyzed statistically. In this report a more accurate procedure has been used to determine from the case histories the duration of illness at the time of admission to the study groups and the total duration of fever. The "clinical classification of severity," based on a review of each patient's record when he was discharged from the hospital, has been replaced by a more objective method for the evaluation of the severity of illness. For these reasons, the data on 10 patients treated in 1944, although presented previously, are included with the new data on 10 patients treated in 1945.\*

*Criteria for the Selection of Patients.* The study groups were composed of 39 male Egyptian patients, ages 18 to 48, suffering from epidemic louse-borne typhus fever. The diagnosis was based on the clinical course, the serologic findings and, in 19 instances, the isolation of *R. prowazeki* from the blood or from normal lice fed on the patients during the febrile period, as indicated in tables 1 and 2. None of the patients had been vaccinated against typhus fever. None gave a history of a previous attack of the disease. All came from the same social stratum. Nearly all were somewhat underweight, but otherwise they appeared to be in good physical condition. At the time of admission to the Typhus Commission Ward, none had evidence of complicating illnesses or conditions. A few of the patients in both the control group and the PABA-treated group were subsequently found to have subclinical schistosomiasis, but no patients were excluded from consideration because of this finding. One of the control patients has been excluded from the analysis because he had active pulmonary tuberculosis. One PABA-treated patient developed an exacerbation of chronic amebic

## \* Tabulation of PABA-treated typhus cases:

First report<sup>12</sup>:

7 patients treated consecutively, 1943

3 miscellaneous cases, 1944

10 treated patients in alternate series, 1944

(form half of group analyzed statistically in Part I, present paper)

## Present paper:

10 treated patients in alternate series, 1945

(form other half of group analyzed statistically in Part I)

60 patients treated at Dachau (1945)

5 miscellaneous cases

Total 95

dysentery during convalescence from his attack of typhus; this patient is included in the analysis.

The patients were in the first week of illness at the time of admission to the study groups. They were placed in the control and PABA-treated groups in automatic rotation. When two patients were found simultaneously, the patient having the lower hospital number was selected for the group requiring the next case. In 1944 this schedule was followed, with the two exceptions noted in an earlier report<sup>12</sup>; in 1945 during most of the study the automatic rotation involved three groups: (1) control; (2) PABA-treated; and (3) special high-calorie diet group. The studies of the patients on the specially supplemented diet are reported in another communication.<sup>16</sup>

The period of the study covered only the few weeks at the peaks of the 1944 and 1945 typhus epidemics in Cairo.

In the group which was treated with PABA all patients received the drug for more than three days in amounts adequate to produce measurable concentrations of diazotizable substances \* in their blood throughout the period of therapy. The method of administering PABA in 1945 was the same as that employed in 1944,<sup>12</sup> except that somewhat larger doses of the drug were given and higher concentrations in the blood were attained.

All of the patients received routine nursing care, a uniform diet, and supportive measures intended to combat specific complications as they developed. Temperatures were taken rectally every four hours in the febrile period and early convalescence.

*Estimation of Duration of Illness.* Typhus patients who have not been sick long enough to become stuporous or delirious can usually recall the hour of the day or night when they became ill. This information was determined for 35 of the 39 patients in this study. Whenever possible, the history given by the patient was checked carefully by talking with his family and by visiting his place of employment. In four instances information from these sources was of value in fixing the time of onset of illness.

The duration of illness at the time each patient was first admitted to the study groups was estimated to the nearest quarter day on the basis of the hour of onset as stated in the history. The duration of fever was estimated in a similar manner, from the onset of illness to the last rectal temperature reading above 37.5° C. An interval of secondary fever occurred in a few of the cases in the PABA-treated group. In the analysis of the data the duration of the secondary fever has been added to that of the primary fever, the total being expressed to the nearest quarter of a day.

*Estimation of Severity of Illness.* In the 1944 report<sup>12</sup> each patient's record was reviewed at the time of his discharge from the ward, and the severity of his illness was classified in one of six groups. Although previously reduced as much as possible, the subjective factors involved in that

\* This point is discussed in a subsequent section of this paper.

TABLE I  
Summary of the Data from 20 Cases Treated with Para-Aminobenzoic Acid (PABA)<sup>1</sup>, Cairo, Egypt, 1944 and 1945

Case No.	Age, Years	Body Weight, Kg.	Duration of Illness When Treatment Was Begun, Days	Duration of Treatment, Days	Total Amount PABA Given, Grams	Maximum Blood Level PABA <sup>2</sup> , mg. %	Lowest WBC/cu. mm.	Maximum N.P.N., mg. % <sup>3</sup>	Rash <sup>4</sup>	Maximum Titers <sup>5</sup>		R. prozone test demonstrated <sup>6</sup>	Duration of Fever, Days	Duration of Secondary Fever, Days	Complications <sup>7</sup>	Final Score <sup>7</sup>
										Weil-Felix (OX19)	Complement Fixation (Epidemic antigen)					
1	32	54.0	1	8½	182	35	5,800	31	+	640	512	Yes	8¾	none	none	8¾
2	23	61.4	1½	6½	168	5	7,500	30	?	640	1,024 NEP	Yes	6¾	none	none	6¾
3	18	63.2	1¾	13	294	27	3,250	45	+	10,240 NEP	80	N.A.	11¼	none	j	12¼
4	20	60.0	2	6	154	15	4,900	24	+	1,280	128	Yes	11½	none	none	11½
5	40	65.0	2¾	5	104	63	3,900	44	0	40	640	N.A.	5¾	none	none	5¾
6	34	48.6	3¾	11	224	40	5,250	46	+	10,240 NEP	320	N.A.	12	none	j	13
7	18	51.8	4	7½	169	35	2,500*	43	+	10,240 NEP	320	N.A.	12½	3¼	none	15¾
8	20	56.0	4¼	4	94	35	5,600	29	+	5,120 NEP	1,024 NEP	Yes	7¼	7	a, e	16¼
9	22	56.8	4¾	6	146	17	5,650	32	+	5,120 NEP	1,024 NEP	Yes	9¾	none	none	9¾
10	28	56.8	4¾	4	100	10	5,100	43	?	2,560	1,024 NEP	Yes	8¼	1¼	none	8½
11	22	65.0	5	8	188	24	3,150	33	+	40	2,560 NEP	N.A.	10½	none	a	11½
12	30	53.2	5	11	195	43	4,200	31	+	5,120 NEP	1,024 NEP	Yes	14¾	none	none	14¾
13	23	47.8	5	5½	93	41	3,250	50	+	negative	negative	N.A.	10½	none	a, b, j, m	33 (died)
14	35	58.2	5½	5	115	12	1,850**	32	+	5,120	1,024 NEP	Yes	8¾	none	none	8¾
15	33	61.4	5¾	11	235	24	5,000	40	+	5,120	640	N.A.	16	1¼	a, e, h	19¼
16	42	58.6	5¾	13	316	52	2,650*	45	+	5,120	640	N.A.	31¼	none	a, e, h, j	24
17	48	56.8	6	6½	148	13	3,350	39	+	80	1,024 NEP	Yes	16¼	none	a, b, d, h	20¼
18	35	50.0	6¼	7	164	33	3,450	46	+	160	1,024 NEP	Yes	12½	2½	j	16
19	27	51.4	6¼	12	238	52	3,450	35	+	320	2,560 NEP	N.A.	19½	none	a	20½
20	20	59.5	6½	8	181	36	3,050	39	+	320	320	N.A.	10½	none	none	10½
Mean	28.5	56.8	4.4	7.9	175.4	30.6	4,100	37.8					12.8		1.6	14.3
S. D.	8.7	5.2	1.7	2.9	62.6	15.7	1,400	7.3					4.3***		3.0#	6.6

classification have been eliminated in the present analysis by computing a final score for each patient which is obtained by adding together the number of days of fever and the number of "complications." The latter term has been selected for convenience to represent those features of the clinical course of typhus which indicate the severity of the disease. Each complication is denoted in subsequent tables by a letter as follows:

- a—delirium
- b—stupor
- c—coma
- d—incontinence of urine and/or feces
- e—pneumonitis
- f—secondary bacterial infections (otitis media, or parotitis, or furunculosis)
- g—gangrene
- h—urinary retention
- i—oliguria (less than 500 c.c. of urine in 24 hours)
- j—blood nonprotein nitrogen (NPN) 45 mg. per 100 c.c. and above
- k—blood nonprotein nitrogen 80 mg. per 100 c.c. and above
- l—systolic blood pressure below 80 mm. Hg
- m—pulse rate above 140 beats per minute, or gallop rhythm.

<sup>1</sup> Arranged according to the day of disease when treatment was begun.

<sup>2</sup> These values signify the highest level found throughout the course of treatment two hours following the preceding dose of PABA.

<sup>3</sup> When high blood levels of PABA were encountered, the total nonprotein nitrogen value has been corrected for the nonprotein nitrogen contributed by the presence of PABA. Values for the blood nonprotein nitrogen of 45 mg. per cent or more are interpreted as evidence for nitrogen retention or azotemia throughout this report.

<sup>4</sup> The rash is classified as follows: 0, none seen at any time; ?, questionably present; +, light; ++, moderate; +++, profuse.

<sup>5</sup> NEP indicates that the end point was not reached, the value being the highest dilution tested.

<sup>6</sup> These symbols are interpreted as follows: (a) delirium; (b) stupor; (c) coma; (d) incontinence of urine and/or feces; (e) pneumonitis; (f) secondary bacterial infections (otitis media, parotitis or furunculosis); (g) gangrene; (h) urinary retention; (i) oliguria (less than 500 c.c. urine in 24 hours); (j) blood nonprotein nitrogen 45 mg. per cent and above; (k) blood nonprotein nitrogen 80 mg. per cent and above; (l) systolic blood pressure below 80 mm. Hg; (m) pulse rate above 140 beats per minute, or gallop rhythm.

<sup>7</sup> For calculation of final score see text.

\* Further treatment of this patient was discontinued because of the low white blood cell count.

\*\* The low white blood cell count developed three days after cessation of treatment.

\*\*\* Mean and standard deviation refer to total fever (primary plus secondary), with maximum set at 20 and fatal case counted as 20. See text for explanation.

# Mean and standard deviation calculated on basis of 13 complications for fatal cases. See text for explanation.

## "R. prowazeki demonstrated" means that the following criteria were satisfied: (a) Demonstration of morphologically typical intracellular coccobacillary forms in bacteria-free yolk sac suspensions and/or cotton rat peritoneal or mediastinal exudates, following inoculation with passage material derived from patient's blood, or from normal lice which were fed on the patient during the febrile period; (b) reciprocal cross immunity with Breinl strain of *R. prowazeki* as tested by fatal challenge doses in cotton rats; (c) development of specific antibodies in sera of cotton rats or guinea pigs following inoculation of material in question. The letters N.A. mean that no attempt was made to isolate rickettsiae.

TABLE II  
Summary of the Data from 19 Alternate Control Cases,<sup>1</sup> Cairo, Egypt, 1944 and 1945

Case No.	Age	Body Weight, Kg.	Duration of Illness When Admitted, Days	Lowest WBC/cu. mm.	Maximum N.P.N., mg. %	Rash <sup>1</sup>	Highest Titer <sup>5</sup>		R. <i>prova-</i> <i>demon-</i> <i>strated</i> ##	Duration of Continuous Fever, Days	Complications <sup>6</sup>	Final Score <sup>7</sup>
							Weil-Felix (OX19)	Complement Fixation (Epidemic Antigen)				
1	21	48.2	3/4	5,950	35	++	40	1,024 NEP	Yes	24 1/4	a, b, d, f	24
2	30	54.1	2 1/4	3,250	45	+	2,560	1,280	N.A.	14 3/4	a, b, d, e, h, j, m	21 3/4
3	30	52.7	2 1/2	4,300	109	++	80	640	Yes	9 1/4	a, b, c, d, i, j, k, l, m	33 (died)
4	21	57.0	2 3/4	9,650	38	++	5,120 NEP	1,280	Yes	16 1/4	a, b, d, h	20 1/4
5	18	54.1	2 3/4	4,450	40	++	40	640	N.A.	15 1/4	e, m	17 1/4
6	18	54.6	3 3/4	5,900	88	++	10,240 NEP	640	N.A.	12 1/4	a, b, c, d, e, h, j, k, l, m	33 (died)
7	26	60.0	3 3/4	3,400	200	++	2,560	negative	Yes	8 3/4	a, b, c, d, h, i, j, k, m	33 (died)
8	22	49.0	4 1/4	14,650	29	++	1,280	640	Yes	28 1/2	a, b, d, f	24
9	46	51.8	4 1/4	6,200	110	++	640	5,120	Yes	17 1/2	a, b, c, d, e, j, k, l, m	33 (died)
10	25	67.3	4 1/2	1,900	50	++	80	2,560 NEP	Yes	26 3/4	a, b, d, h, j, m	26
11	25	49.1	4 3/4	4,900	48	++	2,560	1,280	N.A.	19 1/2	a, d, j, h, m	24 1/2
12	25	55.0	5	4,900	75	++	5,120 NEP	640	Yes	18 1/2	a, b, c, d, f, g, h, j	26 1/2
13	38	57.3	5 1/4	4,100	47	++	10,240 NEP	160	N.A.	12 3/4	a, b, c, j	15 3/4
14	43	58.6	5 1/4	2,550	75	++	2,560	1,280	Yes	12 1/2	a, b, c, e, i, j	33 (died)
15	41	50.5	5 3/4	4,150	63	0	40	160	N.A.	15 1/4	a, b, j, m	33 (died)
16	23	46.4	6 1/4	3,300	33	++	10,240 NEP	640	N.A.	18	a, b, d, m	22
17	24	46.0	6 1/4	4,400	40	++	5,120 NEP	640	N.A.	15 1/2	a, b, d, e, m	19 1/2
18	35	59.1	6 3/4	7,600	42	?	2,560	320	Yes	11 1/2	none	11 1/2
19	20	55.5	7 1/4	3,900	41	+	320	2,560 NEP	N.A.	17 3/4	m	18 3/4
Mean	27.9	54.0	4.4	5,200	63.6					17.9***	6.8#	24.7
S. D.	8.6	5.3	1.7	2,900	41.1					2.7***	4.7#	6.8

<sup>1</sup> For explanation of data in this table see footnotes for table 1.

The febrile period in uncomplicated typhus rarely lasts longer than 20 days. Longer periods of fever are caused by various complications, particularly secondary infections. Since complications contribute independently to the final score, the maximum duration of fever is set arbitrarily at 20 days. In computing the score for a fatal case, it is assumed that such a patient had the maximum duration of fever and the maximum number of complications, the score being 33. Theoretically, a surviving patient could have had a score of 33, but actually this was not found.

*Presentation of Data.* Tables 1 and 2 contain the data for the 39 patients in the alternate treated and control groups. The patients are arranged according to the duration of illness at the time they were admitted to the study groups. Various data, including age, duration of fever, lowest white blood cell count, highest blood nonprotein nitrogen, maximum titer in serologic tests, incidence of complications and final score, are indicated for the control cases. For the treated cases the same data are reported, as well as the duration of PABA therapy, the highest concentration of PABA in the blood, and the total amount of drug given.

Figure 1 shows the temperature curves of the two groups. The points on the curves represent the means of the rectal temperature readings for each day of illness for all the cases in each group. The number of observations contributing to the mean is six times the number of patients, since each

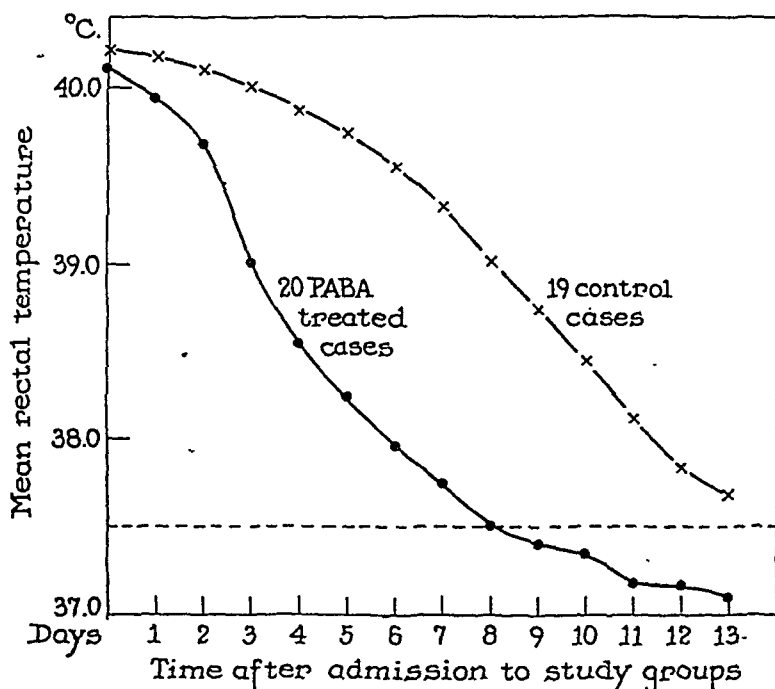


FIG. 1. Comparison of temperatures of 20 PABA-treated patients and 19 alternate control patients, Cairo, Egypt, 1944 and 1945. Mean daily rectal temperatures are plotted for each group, zero day being the day of admission of each patient to the study (the mean duration of illness at the time of admission for both groups was 4.4 days). The temperatures of fatal cases are included up to the last reading before death occurred.

patient had his temperature taken six times daily. The readings observed on the day of admission to the study groups are plotted at the zero point, and the readings on the successive days are indicated for the following 13 days. The fatal cases are included up to the last reading before death. The mean value in the treated group fell below  $37.5^{\circ}$  C. on the eighth day after treatment was begun. The mean value for the control cases had not fallen to that point by the thirteenth day.

### ANALYSIS OF DATA

The 19 patients in the control group had mean values as follows: age, 27.9 years; duration of illness when admitted to the group, 4.4 days; duration of fever, 17.9 days; number of complications, 6.8; final score, 24.7. Six patients in the control group died.

The 20 patients in the PABA-treated group had mean values as follows: age, 28.5 years; duration of illness when treatment began, 4.4 days; duration of fever (primary plus secondary), 12.8 days; number of complications, 1.6; final score, 14.3. One patient in the treated group died.

The scatter of the values about the means for both groups is expressed as the standard deviation (S. D.) shown in tables 1, 2, and 3.

These figures indicate that the control and treated groups were nearly identical as regards mean age and mean duration of illness when admitted, but that there were large differences in duration of fever and number of complications between the two groups. The statistical significance of the differences has been computed using "Student's" *t* test. The results are shown in table 3. The difference in mean duration of fever in two groups

TABLE III

Values of *t* for the Differences between Control and PABA-Treated Groups, Cairo, Egypt, 1944 and 1945, as Regards Duration of Fever, Number of Complications and Final Score

	Means and Standard Deviations		Difference between the Means	Standard Deviations (both groups combined)	" <i>t</i> "*	p
	Control	Treated				
Duration of fever (days)	17.9, 2.7	12.8, 4.3	5.1	4.4	3.6	0.001
Number of complications	6.8, 4.7	1.6, 3.0	5.2	4.7	3.5	<0.01
Final score	24.7, 6.8	14.3, 6.6	10.4	8.4	3.9	<0.001

\* "*t*" calculated in manner described by Mainland "Treatment of Clinical and Laboratory Data," Oliver and Boyd, London, 1938, p. 157.

of this size would be expected to occur by chance only once in approximately 1,000 trials; the difference in number of complications once in more than 100 times; and the difference in score once in more than 1,000 trials. It is highly unlikely, therefore, that the differences were due to chance.

It might be argued that the differences are due to the inclusion of fatal cases with arbitrarily assigned maximum scores. To examine this point, a

comparison of the duration of fevers in the two groups was made in which only surviving patients were considered. This showed 16.9 days for controls and 12.4 days for PABA-treated cases. For this difference  $t$  is 2.97 and  $p$  is less than 0.01. In a similar manner the incidence of complications has been compared in the two groups, counting for the fatal cases only those complications which were noted in each instance, rather than the maximum number. The mean values are 5.2 for controls and 1.1 for PABA treated cases;  $t$  for this difference is 4.20 and  $p$  is less than 0.001. The arbitrary standards used in computing the scores for the fatal cases do not, therefore, give rise to the differences between the two groups. In the following paragraphs other factors are considered which might have contributed to the difference between the control and the PABA-treated groups.

*Age.* The mortality from typhus increases with age. An unequal age distribution between the groups might produce differences in duration of fever, number of complications, and score. To examine this factor more closely, the control and treated patients have been arranged according to age in table 4. It is obvious from inspection of this table that the age distribution is essentially identical in the two groups. The differences in score cannot be attributed to age difference.

TABLE IV  
Comparison of Ages of Control and PABA-Treated Patients,  
Cairo, Egypt, 1944 and 1945

Ages		
Control		Treated
18, 18, 20, 21		18, 18, 20, 20
21, 22, 23, 24		20, 22, 22, 23
25, 25, 25, 26		23, 27, 28
30, 30, 35, 38		30, 32, 33, 34
		35, 35
41, 43, 46		40, 42, 48
Mean	27.9	28.5
S. D.	8.6	8.7

*Duration of Illness at Time of Admission to the Study Groups.* The data in tables 1 and 2 show that the mean duration of illness at the time of admission was identical for the PABA-treated group and the control group. Thus, there is no evidence that the differences in duration of fever and number of complications could be attributed to this factor. However, it is of interest to determine whether, within each group, there was any relation between the duration of illness at the time of admission and the final score.

In figure 2 the final scores of control and PABA-treated cases are plotted against duration of illness at the time of admission. In the control group the points are widely scattered. Calculation shows that the coefficient of correlation,  $r$ , is  $-0.24$ . Thus, in the control group there is no evidence that the duration of illness at the time of admission (up to the end of the



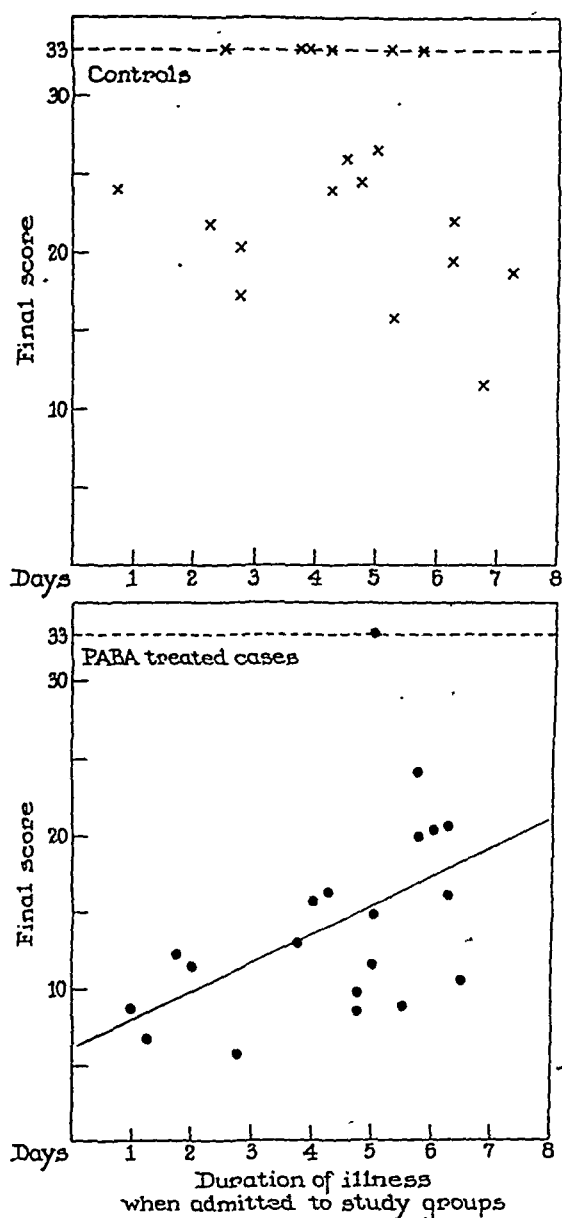


FIG. 2. Comparison of final score and duration of illness when admitted to the study groups. Control patients charted above, PABA-treated patients below. Fatal cases given score of 33.

seventh day) has any relation to the severity as judged by the final score (duration of fever plus number of complications).

On the contrary, however, the points in figure 2 for the PABA-treated cases suggest a definite relationship between the duration of illness when treatment was begun and the final score. The coefficient of correlation,  $r$ , is found to be  $+0.481$ . For this value of  $r$ ,  $p$  lies between 0.05 and 0.02. It may be stated, therefore, that the observed relationship would not be expected to occur by chance. It should be noted in considering this correlation that the patients who were admitted near the end of the first week of illness already had accumulated a higher initial score and that the possibility of a

difference in final score occurring between the control and the treated patients was thereby reduced. By extrapolating the trend of the relationship it appears that the final score in the treated group would attain a value equal to the mean final score of the untreated patients between the tenth and eleventh days. Controlled data on this point are not available, but it is likely that a very large group of patients would be required to evaluate an effect of PABA if treatment were first begun more than eight days after the onset of illness.

*Comparison of Cases Treated in 1944 and 1945.* Since the data in this analysis were obtained in two different seasons, it is important to determine whether there were differences in the severity of the epidemics in the two years, and whether the study groups in the two seasons have comparable values for final scores.

The figures for the entire population of male Egyptian typhus patients, ages 18 to 48, admitted to the general wards of the Cairo Fever Hospital in May and June 1944 (the period covered by the 1944 alternate series) were as follows: 156 cases, 46 deaths (29.5 per cent mortality). For the period covered by the 1945 alternate series (April and May) the figures were: 215 cases, 64 deaths (29.8 per cent mortality). The age distributions were nearly the same in the two periods. It appears that the populations from which the study cases were drawn in 1944 and 1945 were essentially identical as regards mortality.

In the study groups themselves, the mean values for duration of fever and incidence of complications observed in 1944 have been compared with the mean values observed in 1945. No significant differences were present between the control groups in the two years; there is thus no evidence that they were not drawn from the same population.

However, for the PABA-treated group, the mean final score in 1945 was greater than the mean score in 1944. Although the difference in score is not great enough to be statistically significant, it is interesting to note that the mean duration of illness at the time of admission for the 1945 patients was slightly greater than that of the 1944 patients. On the basis of the correlation described in a preceding section the 1945 patients would be expected to have a slightly higher score.

*Mortality.* Six of 19 control patients died; one of 20 treated patients died. A difference of this magnitude would be expected to occur by chance only once in 26 samples of this size.<sup>17</sup>

The pathologic findings in the fatal PABA-treated cases are discussed in the appendix.

*Comparison of White Blood Cell Counts.* It was noted previously<sup>12</sup> that PABA tended to depress the white blood cell count. The data are adequate to permit a rough comparison of the difference in lowest counts in the treated and control groups (tables 1 and 2). The mean of the lowest counts for the 19 alternate controls was 5,200. The mean for the alternate

PABA-treated patients was 4,100. This difference is not statistically significant ( $t = 1.49$ ;  $p$  lies between 0.1 and 0.2). The differential counts recorded at, or close to, the time of the lowest white blood cell count for each patient have been used to calculate the mean values for the differentials, which are shown in table 5. The depression of total white blood cell count in the

TABLE V

Mean Values for the Differential Counts\* of Alternate Treated and Control Groups at, or Close to, the Time of Lowest Recorded White Blood Cell Count, Cairo, Egypt, 1944 and 1945

	Mean of Lowest White Blood Cell Counts	Mean Values of Differential Counts Taken at, or Close to, the Time of Lowest White Blood Cell Count†					
		P	L	M	E	B	Uncl.
19 control patients	5,200	69.9	25.3	1.2	0.6	0.8	2.3
20 PABA-treated patients	4,100	55.1	38.4	1.5	1.2	0.4	3.4
Difference between control and treated	1,100	14.8	13.1	0.3	0.6	0.4	1.1
Standard deviation of both groups combined	2,300	13.6	12.8	1.5	1.4	0.9	
"t" =	1.49	3.4	3.2	0.6	1.3	1.4	
p =	<0.2 >0.1	<0.01	<0.01	<0.6 >0.5	0.2	<0.2 >0.1	

\* The figures are based on numbers of cells in each 100 counted.

† P = polymorphonuclear cells; L = lymphocytes; M = monocytes; E = eosinophiles; B = basophiles; Uncl. = unclassified.

PABA-treated cases was accompanied by a statistically significant reduction in the percentage of polymorphonuclear cells and a similar increase in the percentage of lymphocytes. The differences in percentages of monocytes, eosinophiles, and basophiles were not statistically significant.

*Summary of the Statistical Analysis of the Data.* Thirty-nine male Egyptian patients, aged 18 to 48 years, suffering from proved typhus fever, were studied in the Typhus Commission Ward in the Cairo Fever Hospital, in 1944 and 1945, at the peaks of the epidemics in those seasons. The patients were in their first week of illness when admitted to the study groups. Alternate cases were treated with large amounts of PABA; these patients had shorter fever, fewer complications, and a lower mortality rate than the untreated controls. The differences were found to be statistically significant. Factors which might have been of importance in producing the differences were considered. These were age distribution, duration of illness when admitted to the study groups, and variation in the severity of the epidemics in 1944 and 1945. No evidence was found that these factors contributed to the differences between PABA-treated and control groups.

Within the PABA-treated group itself there was a significant correlation between the duration of illness when therapy was begun and the final score (composed of days of fever plus the number of complications).

## PART II

USE OF PABA IN THE TYPHUS FEVER EPIDEMIC IN THE DACHAU  
CONCENTRATION CAMP IN GERMANY, MAY 1945

In the preceding sections the controlled clinical trial of PABA in typhus fever has been presented in detail. We were convinced by this experience that the drug definitely lessened the severity of the illness when treatment was begun early in the disease and when sufficiently large amounts were given to produce an adequate concentration of the drug in the blood during the entire period of therapy.

In May 1945 an opportunity arose to apply the experience with PABA to the outbreak of typhus fever in the Dachau Concentration Camp in Germany. The United States Seventh Army liberated Dachau on April 29, 1945. The wretchedness and the horrible conditions encountered among the forty thousand inmates of this camp defy description. Starvation, tuberculosis, and typhus fever were claiming more than 100 lives daily at the end of April. The medical staffs of the United States Forces which took over the hospitalization at Dachau made every effort to give the inmates a maximum of help. The attempt was made to vaccinate all of the people in the camp with Cox-type vaccine and to apply DDT anti-lice powder to the clothes and sleeping quarters of everyone in the quarantine zone. At least two-thirds of the inmates received typhus vaccine and nearly all had their clothes dusted. In addition, arrangements were made to treat typhus patients with PABA. It should be emphasized strongly that the use of PABA at Dachau was not undertaken as an experimental study. Despite many difficulties, therapeutic amounts of PABA were administered to 60 male patients who had typhus fever.<sup>18</sup> The data are summarized in table 6.

*Selection of Patients for Treatment.* The attempt was made to treat those patients whose condition suggested that they would run a severe course of typhus fever. The circumstances in the camp made it exceedingly difficult to begin treatment early in the disease. For the majority of patients treatment was not begun until the fifth to the seventh day. The age of the patients varied from 17 to 71 years, with a mean age of 32.6 years. Fifteen of the patients gave their nationality as French, 14 as Hungarian, eight as German, six as Russian, five as Polish, and four as Czechoslovak. Three patients came from Austria, two from the Netherlands, one from Greece, one from Norway, and one from Alsace Lorraine.

*Complicating Conditions at the Time Treatment Was Begun.* Severe malnutrition was noted in 13 patients on their admission for treatment. Other conditions such as edema, diarrhea, hematuria, and azotemia were observed. Pulmonary tuberculosis was known to be present in at least three of the patients.

*Plan of Treatment.* Chemically pure PABA was given by mouth in powder form mixed with a 5 per cent solution of sodium bicarbonate. At

TABLE VI

Summary of the Data from 60 Cases of Louse-Borne Typhus Treated with Para-Aminobenzoic Acid at Dachau Concentration Camp, Dachau, Germany  
May-June 1945<sup>1</sup>

Case No.	Age, Years	Nationality <sup>a</sup>	Duration of Illness when Treatment Began, Days	Duration of Treatment, Days	Total Amount of Para-aminobenzoic Acid Given, Gm.	Maximum Blood Level of Para-aminobenzoic Acid, Mg. %	Lowest W.B.C. per Cu. Mm.	Maximum N.P.N., Mg. %	Rash <sup>4</sup>	Duration of Fever, Days <sup>5</sup>	Maximum Titers <sup>6</sup>		Associated Conditions on Admission <sup>6</sup>	Complicating Conditions Occurring during Hospitalization <sup>6</sup>	Severity of Clinical Course	Typhus Vaccine, Number of Injections <sup>6</sup>	Remarks
											Well-Felix	Complement Fixation					
1	20	Hu.	3	10	191	41	5050	44	++	9	10,240 NEP	40	0	0	mild	2	Strain isolated.
2	29	Cz.	3	8	146	17	2300	41	++	12	5,120	160	0	0	mild	2	
3	37	Pl.	3	9	165	32	3200	54	++	12+3	1,280	80	j, n	f	mild	2*	
4	24	Cz.	3	7	186	41	5200	75	++	12+3	2,560	160	j	0	mild	2	70 grams of PABA I.V. Penicillin for infection.
5	22	Ru.	4	9	165	61	2300	35	++	15+6	320	320	p, x	0	mild	2	
6	36	Gr.	4	8	140	56	3550	34	++	11	5,120	160	0	0	mild	2*	
7	37	Gr.	4	7.5	139	55	4450	—	?	8	1,280	neg.	p	0	mild	2*	
8	47	Hu.	4	7	131	38	4950	60	0	11+2	5,120	320	j	0	moderate	2*	PABA discontinued when febrile, due to shortage of drug.
9	36	Gr.	4	11.5	222	36	3950	61	++	16	10,240 NEP	320	j	e	moderate	1	
10	19	Fr.	4	8	178	31	4100	60	++	9	1,280	160	j	0	moderate	2*	Strain isolated.
11	27	Ru.	4	7.5	223	24	4900	43	0	13	640	80	0	0	mild	2*	
12	22	Hu.	5	10	184	32	4800	42	++	13	10,240 NEP	640	0	0	moderate	2	Strain isolated.
13	26	Hu.	5	5	75	67	2900	54	++	9	10,240 NEP	320	j, p	0	mild	2	Strain isolated. PABA discontinued because of vomiting when patient was afebrile.
14	25	Hu.	5	5	97	40	5350	44	0	7	10,240	640	0	0	mild	2*	Probable enteric fever following typhus.
15	22	Gr.	5	8	133	48	3600	50	0	23	2,560	80	j, p, q	0	mild	2*	
16	23	Fr.	5	7	129	45	3000	50	++	12	10,240 NEP	40	0	0	mild	2*	
17	25	Nr.	5	7	136	31	2150	34	++	10	320	320	j	0	mild	0	
18	24	Hu.	5	8	141	57	3150	55	++	11	10,240 NEP	320	p	0	mild	2*	
19	42	Fr.	5	6	109	38	3700	36	++	10+1	5,120	320	j	j, n	moderate	2*	
20	37	Fr.	5	9.5	174	38	3250	41	?	11+4	1,280	160	p	0	mild	2*	
21	32	Hu.	5	8	115	24	5500	35	++	10+4	10,240 NEP	160	p	0	moderate	2*	Strain isolated.
22	33	Hu.	5	4	99	10	7750	53	++	8	2,560	80	r	0	mild	0	Strain isolated. Sulfadiazine for cellulitis associated with furunculosis in convalescence.
23	30	Hu.	6	9	158	36	4300	43	++	14+8	10,240 NEP	160	j, p	0	mild	2*	
24	18	Gk.	6	8	135	61	2850	38	0	11+1	10,240 NEP	160	0	0	mild	1	Died on 10th day. Autopsy: see appendix.
25	36	Pl.	6	2	48	93+	4500	150	0	10	640	neg.	0	0	mild	—	Chronic alcoholism. I.V. plasma.
26	34	Gr.	6	10	171	66	3550	37	++	14	10,240 NEP	1,280	k, n, s	0	fatal	—	13 days secondary fever associated with chest signs of pneumonitis. X-ray consistent with atypical pneumonitis.
27	27	Gr.	6	3	47	36	1300	36	++	15+4	10,240 NEP	320	0	y	mild	2*	
28	52	Gr.	6	7	98	54	3900	38	++	12+3	1,280	640	t, z	r, z	severe	2*	
29	41	Fr.	6	11	186	56	2450	41	++	14+7	160	132	0	z	mild	2*	
30	32	Fr.	6	3	56	41	1300	38	?	9+13	10,240 NEP	160	r	r	moderate	1	

TABLE VI—Continued

Case No.	Age, Years	Nationality <sup>a</sup>	Duration of Illness when Treatment Began, Days	Duration of Treatment, Days	Total Amount Para-benzoic Acid Given, Gm.	Maximum Blood Level of Para-benzoic Acid, Mg. %	Lowest W.B.C. per Cu. Mm.	Maximum N.P.N. <sup>3</sup> , Mg. %	Rash <sup>4</sup>	Duration of Fever, Days <sup>5</sup>	Maximum Titer <sup>6</sup>		Associated Conditions Occurring during Hospitalization <sup>6</sup>	Complicating Conditions	Severity of Clinical Course	Typhus Vaccine, Number of Injections <sup>9</sup>	Remarks
											Weil-Felix	Complement Fixation					
31	27	Fr.	6	8	127	45	2250	41	+	11	10,240 NEP	160	u	0	mild	2*	Artificial pneumothorax—right lung.
32	26	Fr.	6	8	158	28	5450	40	+	13	10,240 NEP	80	p	0	mild	2*	
33	30	Pl.	7	5	96	30	3750	52	++	12	640	640	j	0	mild	2*	Strain isolated.
34	22	Pl.	7	7	113	55	3100	50	++	11+1	1,280	320	j	0	mild	—	Strain isolated.
35	24	Hu.	7	6.5	124	40	3900	41	?	12	5,120	160	0	0	mild	2*	
36	20	Ru	7	8	152	41	5050	35	++	15	10,240 NEP	320	0	0	moderate	2	Sudden death, 12th day. Autopsy: see appendix.
37	54	An.	7	5	82	41	3150	54	++	12	320	40	j	0	fatal	2	
38	26	Du.	7	6	115	43	4050	38	++	10	1,280	640	0	0	mild	2*	
39	43	Fr.	7	10	211	32	3350	36	++	17+2	5,120	320	0	e	severe	2	
40	25	Fr.	7	11	221	35	3850	42	++	17	10,240 NEP	640	n	e	severe	2	
41	24	Fr.	7	7	120	44	8100	50	++	13	1,280	320	0	j	severe	2*	
42	41	Fr.	7	11	189	41	2150	53	++	14	2,560	640	j	0	moderate	2	
43	58	An.	7	7	146	18	3750	38	++	14	10,240 NEP	160	0	0	moderate	0	
44	21	Cz.	7	11	340	69	5150	90	++	14	10,240 NEP	640	n	0	mild	2	205 gm. PABA I. V. over four days.
45	17	Ru.	7	3	40	63	3750	40	0	13+1	10,240 NEP	640	0	0	mild	2	40 gm. PABA I. V.
46	48	Al.	8	8	143	55	5550	—	++	13+1	320	640	0	0	mild	0	
47	21	Hu.	8	7	128	35	5400	42	++	12+1	10,240 NEP	320	0	0	mild	2	
48	57	Al.	8	9	149	34	1650	34	++	16	320	640	p, r, v	z	moderate	2*	Plasma I. V.
49	30	Du.	8	7	145	35	2700	39	++	14	2,560	160	0	e	moderate	2*	
50	41	Fr.	8	7	132	35	4200	40	++	14	160	80	p	0	mild	2	
51	32	Hu.	9	8	154	52	3000	37	++	15	1,280	160	p	0	moderate	2*	
52	20	Fr.	10	7	118	67	3850	60	++	16	10,240 NEP	320	j, n	e	moderate	2*	
53	32	Hu.	11	12	222	65	4050	36	++	31	320	640	0	d, e	severe	—	Strain isolated. Refused PABA on 3 occasions.
54	71	Ru.	11	10	228	19	3800	44	++	17+1	10,240 NEP	1,280	n, u	0	mild	0	
55	46	Gr.	16	7	97	54	5350	109	++	21+14	10,240 NEP	2,560	k, n, p	f, k, r	severe	2*	TBC right lung. Positive sputum.
56	35	Hu.	3	13	348	45	3600	35	0	27+	2,560	160	u	f	moderate	2	75 grams PABA I. V.
57	31	Cz.	5	11	271	30	2600	41	++	19+	640	160	j, u	e, z	severe	0	Sudden death, 4th hospital day. Autopsy: see appendix.
58	35	Fr.	?	2	41	40	5550	46	++	?	neg.	neg.	j, u	e	fatal	2*	
59	22	Ru.	76	8	189	12	4150	47	++	713	1,280	320	f, n	f, j	severe	2	
60	39	Pl.	76	8	156	45	2600	40	+	712+1	2,560	320	p	0	mild	2*	

Footnotes 1, 2, 3, 4, and 5 as in table 1.

<sup>6</sup> These symbols are interpreted as follows: a, delirium; b, stupor; c, coma; d, incontinence of urine and/or feces; e, pneumonia; f, secondary bacterial infections (otitis media, parotitis or furunculosis); g, gangrene; h, urinary retention; i, oliguria (less than 500 c.c. urine in 24 hours); j, blood nonprotein nitrogen 45 mg. per cent and above; k, blood nonprotein nitrogen 80 mg. per cent and above; l, systolic blood pressure below 80 mm. Hg; m, pulse rate above 140 beats per minute, or gallop rhythm; n, hematuria; p, malnutrition; q, conjunctivitis; r, diarrhea; s, epilepsy; t, cirrhosis, ascites; u, pulmonary TBC; v, hypoproteinemia; w, scabies; x, gun shot wound, left hand; y, convulsions; z, edema; T.P.C., thrombophlebitis.

<sup>7</sup> When a second period of fever occurred, it is indicated by the second figure in the column.

<sup>8</sup> Key to nationality. Al = Alsation, Au = Austrian, Cz = Czechoslovakian, Du = Dutch, Fr = French, Gk = Greek, Gr = German, Hu = Hungarian, Pl = Polish, and Ru = Russian.

<sup>9</sup> 0 = no vaccine, — = doubtful, 1 = 1 c.c., 2 = 2 c.c., 2\* = probably more than 2 c.c. of Cox-type vaccine administered by the U. S. Army. These data were obtained only from questioning each patient. See text for discussion of typhus immunization at Dachau.

Note: The isolation of rickettsial strains from certain patients in this service was performed by feeding a colony of uninfected stock lice on the leg for 7 to 10 days, or by inoculation of ground blood clot into guinea pigs.

least 20 c.c. of bicarbonate solution was given for each gram of drug, but the amount of bicarbonate was increased from time to time depending upon the determination of the pH of freshly voided urine specimens. The majority of patients received the drug every two hours, day and night. At some time during their course of therapy a few patients received the drug at intervals of four hours. The initial dose varied from 4 to 6 gm. and subsequent doses ranged from 1 to 3 gm. depending upon the blood concentration, which was determined at least once every 24 hours in all cases and at intervals of four hours in some. The white blood cells were counted at least once every two days for all patients under treatment. When low counts were found, differential counts were performed as often as possible. Treatment with PABA was continued until the temperature had reached normal levels for 24 hours or longer. A temporary shortage of the drug occurred at one time, interrupting treatment in a few patients who were still febrile. Four patients received varying amounts of the sodium salt of PABA by continuous intravenous infusion. The salt was dissolved in physiological saline solution in concentrations of from 1 to 5 per cent. The longest period of intravenous administration in any patient was four days. The thrombophlebitis which occurred in two patients during this form of therapy probably was attributable to inadequate buffering or improper sterilization of the solutions.

*Supportive Therapy.* Plasma infusions, parenteral saline injections, and specific treatment of secondary bacterial infections with penicillin or sulfonamide drugs were given as conditions required.

*Complications Arising during the Course of Treatment.* After five days of therapy one patient experienced nausea and vomiting; since he had become afebrile PABA was discontinued. Another patient refused further therapy after seven days of treatment. In the remaining 58 cases no serious difficulties were encountered in the oral administration of the drug.

A white blood cell count of less than 3,000 per cubic millimeter was observed in nine patients who were still febrile and receiving PABA; their treatment was continued for one to four days after the low count was noted. Six patients were first found to have counts below 3,000 after PABA therapy had been stopped. The lowest value among the Dachau patients was 1,600, which was found 24 hours after cessation of treatment. The differential showed 62 per cent polymorphonuclear leukocytes at that time.

Under observation none of the patients with leukopenia showed any evidence of secondary infection commonly associated with agranulocytosis. One patient was still febrile but not receiving PABA on the nineteenth day of disease, when it was necessary to transfer him to another hospital, and the ultimate outcome of his illness is not known. The remaining 14 patients with low white counts were all discharged as cured of typhus.

In 24 patients the blood nonprotein nitrogen rose above 45 mg. per 100 c.c. during the course of treatment with PABA, and in two patients micro-

scopic hematuria developed. These findings have been observed frequently in patients with louse-borne typhus who are not receiving PABA.

Physical signs or roentgenographic evidence of pneumonitis were observed in nine of the 60 patients.

A secondary rise in oral temperature above  $37.3^{\circ}$  C. occurred in 19 patients after their temperatures had been normal for at least 24 hours. In seven of the 19 patients this secondary febrile period could be accounted for by such conditions as otitis media, wound infection, abscesses, continuing diarrhea, or pneumonitis. In the remaining 12 patients the cause of fever was obscure. Although the possibility of active pulmonary tuberculosis was not ruled out, the oral temperature was rarely more than  $37.8^{\circ}$  C. and the fever lasted only a short time. It was associated with practically no symptoms. In some of these cases the secondary fever may have been caused by a mild recrudescence of typhus which occurred because PABA was withdrawn prematurely.

*The Severity of the Clinical Course of the Typhus Patients Treated with PABA at Dachau.* It was our impression that the patients at Dachau derived benefit from treatment with PABA. The clinical courses of the 60 patients were classified as follows: 34 mild, 15 moderate, and eight severe. Three patients died. The 60 patients had shorter fever, fewer complications due to typhus, and fewer deaths than would be expected to occur in a group of that size suffering from classical louse-borne typhus fever. The clinical courses of the patients whose treatment was begun early in their illness were milder than those of the patients whose treatment was begun late.

More specific comments on the benefit derived by the patients at Dachau from treatment with PABA are not justified. The use of the drug at Dachau was not intended as an experimental study; there were no alternate control patients. Furthermore, the attempt was made to vaccinate everyone in the camp in the first two weeks of May 1945. Individual vaccination records were not kept. A *typhoid* immunization program was carried out simultaneously. Many of the patients admitted for treatment with PABA did not know accurately, if at all, how much *typhus* vaccine they had received. Probably most of the 60 patients listed in table 6 received one or more doses of this vaccine. In almost all instances, however, the patients were in the incubation period of typhus at the time they were vaccinated. There is only meager evidence relating to the effect of administering Cox-type vaccine in the incubation period of typhus.<sup>19</sup> It is possible that the vaccination program at Dachau reduced the severity of the cases in the entire camp. The precise figures are not known, but the overall mortality from typhus fever at Dachau was approximately 10 per cent for the cases under the care of the United States Army Medical Officers in May and June 1945.

*Toxicity of PABA.* In spite of their relatively poor physical condition, the 60 typhus patients who were treated at Dachau tolerated PABA remarkably well. It was not necessary to interrupt therapy during the febrile period



because of nausea and vomiting or leukopenia. Some patients received more than 250 grams of the drug in the course of several days of treatment, and concentrations in the blood, measured two hours after the preceding dose of PABA, were higher than 60 mg. per 100 c.c. in several instances. There were no clinical findings in this group of patients which were interpreted as evidence of toxic reactions to PABA, other than the depression of the white blood cell count. In one of the three fatal cases the kidneys showed microscopic evidence of a nephrosis. The significance of this finding is discussed in the next section.

### CLINICAL SUMMARY OF THE FATAL CASES

The gross and microscopic findings in the fatal cases are described in the Appendix. Three of the four patients presented the clinical features of classical louse-borne typhus (case 13, table 1, and cases 37 and 58 in table 6); they were febrile at the time of death. Throughout hospitalization they had tolerated PABA therapy well. Two of them (no. 37 and no. 58) were considered to be almost convalescent. They died suddenly in bed with no warning. Patient no. 13 became progressively worse during treatment, with increasing rash, delirium, and rising blood nonprotein nitrogen. However, he continued to take the drug until the time of death, the immediate cause of which appeared to be respiratory failure.

The fourth patient who died (no. 25, table 6) showed no rash. In other respects his clinical illness was consistent with typhus fever as complicated by familial epilepsy. He had suffered periodic convulsions from the age of 10. After the administration of 38 gm. of PABA over a period of 36 hours, he experienced several convulsive seizures. The blood nonprotein nitrogen was first determined at this time and found to be 140 mg. per 100 c.c. At the same time the blood concentration of PABA was above 90 mg. per 100 c.c. Therapy was discontinued at once. Nine hours after the first convulsive seizure the patient lapsed into coma; he died 11 hours later. In our opinion the high blood level of PABA obtained in this case after 36 hours of therapy and the greatly elevated blood nonprotein nitrogen were due to pre-existing renal disease. It seems improbable that the severe kidney lesions found at autopsy could have been the result of PABA therapy of such short duration. This case illustrates the importance of a knowledge of renal function in patients receiving PABA and the necessity for frequent determination of the concentration of the drug in the blood. Further consideration of this aspect of treatment is dealt with later in this report.

### MISCELLANEOUS PATIENTS TREATED WITH PABA

In addition to the 20 patients whose cases are presented in the first report<sup>12</sup> and the 70 additional patients discussed in the preceding sections of this paper (see footnote on page 2 for tabulation of cases), we have treated

a miscellaneous group of five typhus patients. In this group there were three Egyptians and two Americans. In four patients the illness was mild, and possibly PABA therapy may have been of some benefit. No definite statement can be made, however, since the time of onset of illness was not known in two instances, and in the other two cases there had been repeated vaccinations against typhus before the onset of illness.

The fifth typhus patient in this miscellaneous group was started on treatment on the third day of illness. He was highly uncoöperative and refused therapy after less than two days of treatment. For that reason he was transferred to the general wards of the Cairo Fever Hospital where he developed the characteristic clinical course of typhus fever and died on the tenth day.

A few patients with diseases other than typhus were also given PABA: one patient with malaria, one with typhoid fever, and two with fever of unknown origin. PABA had no apparent effect on the course of malaria or typhoid. There were no untoward reactions observed in this group.

### PART III

#### POINTS OF IMPORTANCE IN THE USE OF PABA IN HUMAN RICKETTSIAL INFECTIONS

On the basis of our experience with PABA in the treatment of 95 patients with typhus fever and 18 patients with tsutsugamushi disease, we wish to discuss several points of importance in the administration of this substance in human rickettsial infections.

*Importance of Early Treatment.* Good results are to be expected from PABA treatment only when therapy is begun *early* in the clinical course of typhus fever or tsutsugamushi disease.\* The trend in figure 2 suggests that little or no benefit from therapy is likely to be observed when treatment is started after the eighth day of illness. Epidemiologic considerations may be of great value in making a presumptive diagnosis and in starting treatment before the characteristic rash appears or before the usual serologic tests give any help in diagnosis. When the suspicion of a rickettsial infection exists, in the absence of the contraindications mentioned in a later paragraph, we recommend that PABA therapy be initiated without delay.

*Optimum Concentration of PABA.* It is impossible to state from our clinical experience precisely what the optimum concentration of PABA should be for the various rickettsial infections. Some of the PABA is converted in the body to *para-aminohippuric acid*, which has been found to be entirely inert against *R. prowazeki*, *R. mooseri*, and *R. orientalis* in experimental infections.<sup>5</sup> Analyses made with Mirick's soil bacillus<sup>20</sup> in a few

\* The same statement probably can be made with regard to the use of PABA for Rocky Mountain spotted fever, if, as anticipated, further clinical experience with PABA in that disease is in accord with the results of the therapy of experimental spotted fever in guinea pigs and in embryonated eggs<sup>11, 4</sup> (see addendum).

instances suggested that free PABA accounted for about four-fifths of the diazotizable substances<sup>5</sup> in the serum of patients when the total concentration was 15 to 20 mg. per 100 c.c. It has been observed repeatedly that the minimum concentration of PABA required to achieve inhibition of multiplication in embryonated eggs is approximately 5 mg. per 100 c.c. for *R. prowazeki* and *R. mooseri*, but that a concentration of at least 35 mg. per 100 c.c. is required to inhibit the multiplication of *R. orientalis*.<sup>5</sup>

In the absence of more accurate information, we recommend that sufficient PABA be given to attain promptly, and to maintain thereafter for the entire period of therapy, a blood concentration of PABA (as free diazotizable substance measured against a standard of PABA) of 10 to 20 mg. per 100 c.c. for patients suffering from typhus fever, and 35 to 40 mg. per 100 c.c. for patients suffering from tsutsugamushi disease or Rocky Mountain spotted fever.

*Form of PABA.* The PABA should be chemically pure, either as the acid or the sodium salt. The pure compounds are almost entirely colorless and odorless in powder form.\* In solution a faintly brownish color may be present. At least equimolar amounts of sodium bicarbonate should be given with each dose of the free acid (12.5 c.c. of a 5 per cent solution of sodium bicarbonate for each gram of PABA). The amount of bicarbonate should be increased as required to maintain the urine neutral or alkaline in reaction. In most instances it has been our practice to mix the powder (acid PABA) with 5 per cent solution of sodium bicarbonate at the bedside immediately before each dose. After drinking this mixture the patients received 100 c.c. or more of water.

One of the authors (J. C. S.) with Dr. E. C. Curnen has used a 10 per cent solution of the sodium salt of para-aminobenzoic acid, adjusted to a pH of 7.0 for treatment of a patient suffering from typhus which was contracted in the laboratory. This form of administration eliminated the necessity of mixing the powdered PABA with 5 per cent sodium bicarbonate solution before each dose. The 10 per cent solution of the sodium salt was made up in bulk and stored in the cold. The patient who received this form of therapy decidedly preferred it to the mixture of acid PABA with bicarbonate solution. When sodium para-aminobenzoate solution was administered, no bicarbonate solution was necessary unless the urine became acid.

*The Schedule of Dosage.* Since PABA is rapidly excreted in the urine it is necessary to administer this drug at frequent intervals throughout the 24-hour period. After many trials the most satisfactory schedule for oral administration was found to be as follows: The initial dose was roughly 0.05 gm. per pound of body weight, i.e., 8 gm. for a patient weighing 160 pounds. This was followed by a dose of 1 to 3 gm. *every two hours day and night* throughout the course of treatment. It is imperative to measure the

\* The para-aminobenzoic acid and sodium para-aminobenzoate used for the treatment of the patients considered in this report were obtained by the United States of America Typhus Commission from the Eastman Kodak Company, Rochester, New York.

blood concentration at frequent intervals, particularly in cases where appreciable fluctuations in fluid intake and urine output occur from day to day, or in patients with azotemia. Whenever circumstances permitted, it was our practice to measure the blood concentration every four hours for the first 24 hours of treatment. For determination of blood levels, venipunctures were performed just prior to a dose of the drug, that is, two hours following the last dose. Since the blood concentration rises and falls rapidly after each dose of PABA, measurements of the blood concentration two hours after the previous dose represent the lowest concentrations during that interval. Although in some patients it may be desirable to continue measurements of the blood concentration of the drug at intervals of four hours throughout the course of treatment, this usually is not necessary, provided that renal insufficiency is not present, that the urine output and fluid intake are reasonably constant from day to day, and that the two-hour schedule of dosage is strictly observed. Satisfactory blood levels can be maintained after the first 24 hours of treatment by measuring the blood concentration just before each 8:00 a.m. dose. Evidence obtained in the treatment of experimental rickettsial infections has shown that *the most important factor in successful treatment is the maintenance of the concentration of PABA consistently at or above 10 mg. per 100 c.c. of blood for R. prowazeki or 35 mg. per 100 c.c. for R. orientalis*. Because of this fact and because of the rapid elimination of the drug from the body, we advise that frequent determinations be made throughout the entire course of treatment in order to adjust the dosage as required to attain effective blood concentrations.

*Parenteral Administration.* Injections of 25 c.c. of a 20 per cent solution of sodium para-aminobenzoate in physiological saline adjusted to a pH of 7.0 were given intramuscularly to several patients at intervals of four hours. This solution was sterilized by filtering through a Seitz filter. Determinations of the blood concentration at intervals of two hours in these patients showed somewhat erratic values. This method of administration, although well tolerated, was not considered as successful as the oral route.

The administration of chemically pure sodium para-aminobenzoate in a 2 to 5 per cent solution of physiological saline by constant intravenous drip may be considered for patients who cannot take the drug by mouth. In our experience with four patients at Dachau, when a constant rate of flow over the 24-hour period was achieved, the fluctuation in the blood concentration of the drug was negligible. The rate of flow was adjusted to permit the infusion of 25 to 30 gm. of the drug in 24 hours. The difficulties encountered by the intravenous form of therapy were chiefly those attendant upon any prolonged intravenous infusion under field conditions. Under more satisfactory hospital conditions we believe that the intravenous administration of pyrogen-free buffered solutions of chemically pure sodium para-aminobenzoate would be a valuable adjunct to oral therapy for certain patients.

*Duration of Treatment.* In the absence of complications arising during treatment, the administration of PABA to patients with rickettsial infections should be continued until the temperature has been normal for at least 48 hours. If the drug is stopped before this time in the treatment of typhus, a secondary rise in temperature lasting from a few hours to several days may be encountered. In the absence of obvious complications this secondary febrile period probably represents a mild recrudescence of the disease. Premature withdrawal of the drug in the treatment of tsutsugamushi disease was followed by the recurrence of fever and characteristic lymphadenopathy.<sup>13</sup>

*The Importance of Reaction of the Urine during Treatment.* The administration of large amounts of PABA to patients whose urine is acid in reaction may result in precipitation of crystals of PABA in the kidney tubules. Therefore, it must be emphasized strongly that whenever this compound is given, steps must be taken to insure alkaline or neutral reactions in the urine. The pH of the urine should be tested with nitrazine paper at least twice daily as long as patients have measurable concentration of the drug in the blood. Usually it has been found that when 13 to 20 c.c. of a 5 per cent solution of sodium bicarbonate is given with each gram of PABA the pH of the urine will remain at 7.0 or higher. In some cases, however, it may be necessary to increase the amount of bicarbonate solution in order to render the urine neutral or alkaline in reaction. This is particularly the case in patients with azotemia. Under the regimen of bicarbonate administration outlined above, crystals were not found in the urine of patients treated with PABA. Signs of renal involvement, such as azotemia or hematuria, were less frequent and less severe in the treated than in the untreated typhus patients.\*

*The Treatment of Secondary Bacterial Infections in Patients Receiving PABA Therapy.* In our opinion the presence of secondary bacterial infections does not contraindicate PABA therapy. The choice of chemotherapeutic agents for the treatment of complicating bacterial infections during PABA therapy is important. Sulfonamide drugs appear to exert a deleterious effect in experimental rickettsial infections. The action of these drugs on bacteria is inhibited in vitro by the presence of even moderate concentrations of PABA. Sulfonamides should not be employed during the acute febrile phase of the rickettsial disease (first 14 days after clinical onset) or in the presence of measurable concentrations of PABA in the blood. Penicillin is the drug of choice if organisms susceptible to its action are the cause of bacterial infections in typhus or tsutsugamushi disease. Penicillin should be used to supplement but not to replace PABA.

*The White Blood Cell Count.* The occurrence of leukopenia in some typhus patients treated with PABA makes it necessary to count the white blood cells at frequent intervals during the course of therapy. We recom-

\* Two of the authors, C. Z. and N. A. T., observed that the urine of some patients under treatment with PABA contained reducing substances. The significance of this finding was not investigated as a part of the study here reported.

mend that white cell counts be performed on every patient daily from the start of therapy until the third or fourth day after treatment is discontinued. When counts fall below 3,000 the percentage of polymorphonuclear leukocytes should be ascertained.

*Contraindications to Treatment with PABA.* Until additional experience is gained from the therapeutic use of PABA we suggest that the fall of the white blood cell count below 3,000 per cu. mm., or the reduction of polymorphonuclear cells to less than 25 per cent during treatment be regarded as a contraindication to further therapy. In each case the clinician must decide whether a falling white count is of more serious prognostic import than the withdrawal of the inhibiting effect of PABA on the rickettsiae.

If PABA crystals appear in the urine the administration of the drug should be stopped at once.

Considerable care should be exercised in giving PABA by mouth to patients who are too weak to swallow properly. Aspiration of PABA may be followed by severe tracheobronchitis.

PABA therapy probably is not indicated for typhus patients under 40 years of age who have been adequately vaccinated,<sup>19</sup> except in cases where the clinical condition at the time of hospitalization suggests that they will become severely ill. In cases of suspected tsutsugamushi disease PABA should be administered regardless of a history of previous vaccination, since there is no evidence that vaccines prepared from *R. orientalis* have any effect on the course of the disease in humans.

In our opinion, the presence of renal insufficiency prior to treatment, or its appearance during the course of therapy is not a reason for withholding or discontinuing PABA provided that the blood concentration is determined frequently, that adjustments in dosage are made accordingly, and that the urine is neutral or alkaline in reaction.

#### SUMMARY AND CONCLUSIONS

From 1943 to 1945 large amounts of PABA were administered to 95 typhus patients of various nationalities (see footnote on page 2). Twenty of the 95 patients were Egyptian males observed in a controlled study in which treatment was begun before the eighth day of illness. Analysis of the results shows statistically significant differences between the PABA-treated and the untreated groups as regards duration of fever, incidence of complications, and mortality. The evidence suggests that treatment begun early in the first week of illness was more effective than treatment begun late in the first week of illness.

Attention is directed to important points in the use of PABA. The form, route of administration, periodicity of dosage, and duration of treatment are discussed. Emphasis is placed on the importance of attaining promptly and maintaining throughout the course of therapy a concentration of the drug in the blood above 10 mg. per 100 c.c. for *R. prowazeki* and 35

mg. per 100 c.c. for *R. orientalis*. It is stressed that the urine must be kept neutral or alkaline in reaction during treatment. The transient lowering of the white blood cell count observed in some patients was the only definite evidence of toxic reaction to PABA.

The pathologic material from four fatal cases of typhus treated with PABA showed no lesions which were regarded as evidence of poisoning with the drug. One fatal case showed nephrosis of uncertain etiology.

It is pointed out that secondary bacterial infections do not preclude the use of PABA for rickettsial diseases. Penicillin is advocated to supplement PABA in the treatment of secondary infections.

The initiation or continuance of PABA therapy is regarded as contra-indicated under the following circumstances: (a) if crystals appear in the urine; (b) if the white blood cell count falls below 3,000 per cu. mm.; (c) if the polymorphonuclear leukocytes are reduced to less than 25 per cent of the total white blood cell count.

#### ADDENDUM

Four clinical reports on the use of PABA appeared after this manuscript was prepared for publication. Maroney, Davis, and Scott reported successful treatment of one patient with Rocky Mountain spotted fever; Flinn, Howard, Todd, and Scott described 10 patients with that disease who were given PABA with favorable effects in nine cases. Smith reported the use of PABA for 27 cases of murine typhus; Levy and Arnold used PABA for six cases of murine typhus with apparently beneficial results. Woodward (personal communication) has collected data on 15 patients with Rocky Mountain spotted fever who appeared to respond to PABA therapy.

1. MARONEY, J. W., DAVIS, H. C., and SCOTT, E. G.: Rocky Mountain spotted fever: a case treated with p-aminobenzoic acid, Del. State Med. Jr., 1946, xviii, 104-106.
2. FLINN, L. B., HOWARD, J. W., TODD, C. W., and SCOTT, E. G.: Para-aminobenzoic acid treatment of Rocky Mountain spotted fever, Jr. Am. Med. Assoc., 1946, cxxxii, 911-915.
3. SMITH, P. K.: The use of para-aminobenzoic acid in endemic (murine) typhus, Jr. Am. Med. Assoc., 1946, cxxxii, 1114-1117.
4. LEVY, M. D., and ARNOLD, W. T.: Para-aminobenzoic acid in treatment of endemic typhus fever, Texas State Jr. Med., 1946, xlii, 314-315. Abstr., Jr. Am. Med. Assoc., 1946, cxxxii, 888.

#### APPENDIX

Summary of the important gross and microscopic pathologic findings in three cases of typhus fever treated with para-aminobenzoic acid.

Case 25, Table 6. Gross anatomical diagnosis: \*

1. Malnutrition.
2. Congestion of the lungs, bilateral.
3. Myocarditis, acute.
4. Hepatopathy, type to be determined.
5. Nephropathy, type to be determined.
6. Cystitis, acute.

\* Autopsy performed by Capt. Ralph M. Schwartz, M.C., Laboratory Officer, 116 Evacuation Hospital, United States Army. Histologic examination of the tissues on cases No. 25, 37, and 38 was done by Capt. Joseph G. Rothenburg, Chief of Pathology, First Medical Laboratory, United States Army.

The *heart* shows a diffuse infiltration of the interstitial tissues by histiocytes, plasma cells, and myelocytes. There is also a diffuse infiltration of epicardial and endocardial tissues. The *liver* shows many areas of focal necrosis occurring in all parts of the lobules, composed of mononuclear cells and nuclear debris. The sinusoids are congested. A large number of convoluted and collecting tubules of the *kidney* are filled with red cells. Some tubules contain pigmented and hyaline casts. The subcapular spaces also contain blood and some are filled with protein precipitate. No inflammatory lesions of the glomeruli are seen. A few foci of lymphocytes are present in the interstitial and perivascular tissues. The head was not examined.

Case 37, Table 6. Gross anatomical diagnosis: †

1. Petechial rash, right axilla and chest.
2. Pulmonary edema.
3. Myocarditis, type and cause undetermined.
4. Lymphoid hyperplasia of mesenteric nodes and gastrointestinal tract.

Sections from the *heart* show a severe degree of inflammatory reaction in the interstitial tissues with lymphocytes, plasma cells, and edema. The myocardial fibers appear atrophic. No vascular lesions of the myocardium are noted. The *lung* parenchyma appears hyperemic, and few intra-alveolar hemorrhages are seen. The small bronchi contain a mucinous exudate in which are pigmented macrophages. The capsular spaces of the *kidneys* contain granules and strands of pink staining material. The cytoplasm of the tubular epithelium appears granular and foamy. The blood vessels are congested. The *brain* shows some degree of satellitosis with infiltration of glial cells. No vascular lesions, petechiae, or foci of necrosis are seen.

Case 58, Table 6. Gross anatomical diagnosis: \*

1. Hemorrhages (petechial) in the skin, basal ganglia, renal pelvis, ureters.
2. Myocarditis, acute moderate.
3. Pulmonary tuberculosis with cavitation in right upper lobe, recent, severe.
4. Pulmonary edema, moderate.
5. Atheromatosis of aorta, innominate, subclavian, carotid and coronary arteries, moderate.

The *heart* shows a diffuse infiltration of the interstitial tissues with histiocytes, lymphocytes and plasma cells. The perivascular tissues are but slightly involved. In scattered foci, compression and atrophy of the muscle fibers are present. One arteriole is seen showing inflammatory changes with thrombosis. The *lung* sections show an encapsulated, caseated tuberculous focus. The interlobular septa are thickened and infiltrated with lymphocytes. Areas of intra-alveolar hemorrhage and bronchopneumonia with polynuclear-leukocytic exudate are present. The *liver* sections show sinusoids containing polynuclear leukocytes. The portal triads are infiltrated with lymphocytes and histiocytes. The *kidneys* show isolated foci of interstitial lymphocytic infiltration. The tubular epithelium appears flattened and the cytoplasm granular. The walls of several of the arcuate vessels show invasion by lymphocytes and eosinophiles. The wall of one small artery of the *brain* shows infiltration with mononuclear and polynuclear leukocytes.

Case 13, Table 1. The pathologic findings, gross and microscopic, were typical of typhus fever. The detailed report will appear in another communication by Dr. McAllister.

† Autopsy performed by Capt. William S. Branning, M.C., of the 127th Evacuation Hospital.

\* Autopsy performed by Major R. Kimball, First Medical Laboratory, United States Army.



Grateful appreciation is expressed to Dr. S. Burt Wolbach, Shattuck Professor of Pathology, Harvard Medical School, who has kindly reviewed the available microscopic material from Cases 25, 37, and 58. In his opinion the microscopic lesions in the myocardium in all of these cases are typical of louse-borne typhus. No lesions are seen in the liver or kidney which can be ascribed to possible poisoning by para-aminobenzoic acid, with the exception of the kidneys of Patient 25, which show tubular degeneration frequently referred to as nephrosis.

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#### BIBLIOGRAPHY

1. SNYDER, J. C., MAIER, J., and ANDERSON, C. R.: Report to the Division of Medical Sciences, National Research Council, Washington, D. C., December 26, 1942.
2. HAMILTON, H. L., PLOTZ, H., and SMADEL, J. E.: Effect of p-aminobenzoic acid on the growth of typhus rickettsiae in the yolk sac of the infected chick embryo, *Proc. Soc. Exper. Biol. and Med.*, 1945, lviii, 255-262.
3. GREIFF, D., PINKERTON, H., and MORAGUES, V.: Effect of enzyme inhibitors and activators on the multiplication of typhus rickettsiae: I. Penicillin, p-aminobenzoic acid, sodium fluoride, and vitamins of the B group, *Jr. Exper. Med.*, 1944, lxxx, 561-574.
4. HAMILTON, H. L.: Effect of p-aminobenzoic acid on growth of rickettsiae and elementary bodies, with observations on mode of action, *Proc. Soc. Exper. Biol. and Med.*, 1945, lix, 220-226.
5. SNYDER, J. C., and STEVENS, D. A.: Paper in preparation.
6. FOX, J. P., and SNYDER, J. C.: Paper in preparation.
7. SNYDER, J. C., and ZARAFONETIS, C. J. D.: Effects of para-aminobenzoic acid in experimental tsutsugamushi disease (scrub typhus), *Proc. Soc. Exper. Biol. and Med.*, 1945, lx, 115-117.
8. MURRAY, E. S., ZARAFONETIS, C. J. D., and SNYDER, J. C.: Further report on effect of para-aminobenzoic acid in experimental tsutsugamushi disease (scrub typhus), *Proc. Soc. Exper. Biol. and Med.*, 1945, lx, 80-84.
9. ZARAFONETIS, C. J. D., SNYDER, J. C., and MURRAY, E. S.: Immunity following para-aminobenzoic acid therapy in experimental tsutsugamushi disease (scrub typhus), *Proc. Soc. Exper. Biol. and Med.*, 1946, lxi, 240-242.
10. SNYDER, J. C.: Unpublished observations.

11. ANIGSTEIN, L., and BADER, M. N.: Para-aminobenzoic acid—its effectiveness in spotted fever in guinea pigs, *Science*, 1945, ci, 591-592.
12. YEOMANS, A., SNYDER, J. C., MURRAY, E. S., ZARAFONETIS, C. J. D., and ECKE, R. S.: The therapeutic effect of para-aminobenzoic acid in louse-borne typhus fever, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 349-356.
13. TIERNEY, N. A.: Effect of para-aminobenzoic acid in tsutsugamushi disease, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 280-285.
14. ROSE, H. M., DUANE, R. B., and FISCHER, E. E.: The treatment of spotted fever with para-aminobenzoic acid, *Jr. Am. Med. Assoc.*, 1945, cxxxix, 1160-1161.
15. BAYNE-JONES, S.: The United States of America Typhus Commission, *Army Med. Bull.*, 1943, No. 68: 4-15.
16. TIERNEY, N. A., and YEOMANS, A.: Metabolic studies in louse-borne typhus, *Jr. Clin. Invest.*, in press.
17. FISHER, R. A.: Statistical methods for research workers, 1936, Oliver and Boyd, London, Sixth edition, pp. 100-102.
18. YEOMANS, A., CLEMENT, D. H., ZARAFONETIS, C. J. D., PHILLIPS, R. A., and SNYDER, J. C.: Activities of the U. S. A. Typhus Commission at Dachau Concentration Camp, 10 May to 10 June 1945, Report to the Director of the U. S. A. Typhus Commission.
19. ECKE, R. S., GILLIAM, A. G., SNYDER, J. C., YEOMANS, A., ZARAFONETIS, C. J. D., and MURRAY, E. S.: The effect of Cox-type vaccine on louse-borne typhus fever, *Am. Jr. Trop. Med.*, 1945, xxv, 447-462.
20. MIRICK, G. S.: The oxidation of p-aminobenzoic acid and anthranilic acid by specifically adapted enzymes of a soil bacillus, *Jr. Exper. Med.*, 1943, lxxviii, 255-272.

# REPORT OF AN OUTBREAK OF Q FEVER AT THE NATIONAL INSTITUTE OF HEALTH. I. CLINICAL FEATURES \*

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At the end of the first week of February 1946, a febrile illness began to appear among the workers in Building No. 5 \* of the National Institute of Health where research was being done on the rickettsia of Q fever. Eighteen cases occurred in an explosive manner between February 6 and February 11, 1946. By May 31 the total number of cases reached 47. This paper deals with the clinical characteristics shown by 45 of the 47 cases.

Epidemiological <sup>1</sup> and laboratory <sup>2</sup> aspects of the outbreak are considered in the other papers in this series. The recent report of a number of cases of Q fever in packing houses, stockyard, and railroad employees in Texas,<sup>3</sup> the identification of a disease occurring widely in certain populations of Italy <sup>4</sup> and the Balkan States <sup>5</sup> as Q fever, and the report of a case from Panama <sup>6</sup> indicate that the illness is more prevalent than has been generally recognized.

This disease was first described in 1937 by Derrick <sup>7</sup> as occurring among meat workers in Brisbane, Queensland, Australia. The clinical features of the nine cases reported were sudden onset, severe headache, slow pulse rate, and normal white cell count. Pneumonitis was not described in these patients. A rickettsia was isolated from these cases and given the name of *Rickettsia burneti* <sup>8</sup> by Derrick.

In 1938, Davis and Cox <sup>9</sup> reported the isolation of a filter-passing infectious agent from *Dermacentor andersoni* collected in Montana. Cox <sup>10</sup> described the rickettsia-like characteristics of the organism and suggested the name *Rickettsia diaporica* <sup>11</sup> for the organism and the name American Q Fever <sup>12</sup> for the disease. The clinical features of a case contracted in a Montana laboratory <sup>13</sup> were similar to those described in Australia and those reported below. *Rickettsia diaporica* and *Rickettsia burneti* were found by Burnet and Freeman,<sup>14</sup> and Dyer <sup>15</sup> to be immunologically indistinguishable.

Burnet and Freeman <sup>16</sup> described a series of mild or subclinical laboratory infections with the rickettsia of Q fever. Hornibrook and Nelson <sup>17</sup> reported a series of cases in 1940 in which a pneumonitis was recognized for the first

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\* Building No. 5 is one of 8 buildings which house the Bethesda laboratories of the National Institute of Health. In this building are the Division of Infectious Diseases, Division of Biologics Control, and a dental unit of the Division of Physiology.

time. The similarity of these cases to those now called primary atypical pneumonia was pointed out by Dyer, Topping, and Bengtson.<sup>18</sup> The pathology of this illness was described by Lillie, Perrin and Armstrong.<sup>19</sup>

The diagnosis of Q fever was made during the 1946 outbreak when either of the two following criteria was fulfilled:

1. A rise in titer for Q fever in the complement fixation test during the convalescent stage of the illness.

2. When no sera were obtained during the acute stage of the illness, a strongly positive reaction for Q fever in the complement fixation test during the convalescent stage of the illness was considered as confirming the diagnosis. Most of the cases fulfilled the first criterion. A few patients who were suspected of having Q fever did not develop significant titers in the complement fixation test and have not been included in this study.<sup>1</sup>

Fifteen cases were hospitalized and thoroughly studied. The remaining 30 cases could not be as thoroughly studied; however, all but a few had histories, physical examinations, and complement fixation reactions during the acute stage of the illness and chest roentgen-rays and laboratory studies during their convalescence.

The incubation period ranged from 12 to 23 days.<sup>1</sup> Cases occurred in all categories of the personnel working in Building No. 5. There were 13 women and 32 men in the series studied; their ages were from 18 to 64.

One of the features of the illness was definite prodromal symptoms lasting in most cases one-half to one day. These symptoms were headache, malaise, generalized aching, anorexia, nausea, vomiting, chest pain, backache, and burning of the eyes. One patient gave a history of headache for three weeks, cough for two weeks, malaise for five days, and burning of his eyes for four days prior to the onset of his fever. The symptoms in some of the cases with prolonged prodromata could have been caused by unrelated upper respiratory infections. Headache, malaise, and aching were the most common prodromal symptoms.

According to the clinical findings, the 45 patients can be divided into two groups: (1) 13 cases with clinical or roentgen-ray evidence of pneumonitis or with symptoms suggesting pneumonitis; (2) 32 cases without clinical or roentgen-ray evidence of pneumonitis or without symptoms suggesting pneumonitis. In the latter group the severity of the disease varied markedly. Six of the patients continued work because of the mildness of their symptoms or because they disregarded more severe symptoms. Three of the patients without pneumonitis were hospitalized, one of whom had a moderately severe form of the disease.

As in the previously reported cases,<sup>7</sup> headache was a prominent symptom. It was most commonly frontal and some patients also complained of occipital headache which was accompanied, in several cases, by stiffness of the neck. In none of the patients was this sign marked enough to indicate a lumbar puncture. The headache was variously described as "severe," "pounding,"

and "bad." There was often increase in the severity of the headache during coughing. One patient stated that it felt like the "top of my head was coming off when I coughed." Chills, chilly sensations, fever, and often sweating occurred in a large number of patients. As in cases previously reported,<sup>7</sup> some of the sweating might have been caused by antipyretics. The highest recorded temperature after a chill was 106° F. Fever occurred in a few cases without chills or sweats. The fever lasted from one to 15 days, the average being about six days. Three patients apparently had no fever.

TABLE I

Tabulation of Symptoms and Signs in 45 Cases of Q Fever

*Symptoms*

Headache.....	34
Generalized aching.....	20
Cough.....	15
Chest pain or discomfort.....	12
Nausea and/or vomiting.....	10
Burning of eyes and/or lacrimation.....	6
Bloody sputum.....	5
Abdominal pain.....	3
Diarrhea.....	2
Constipation.....	2
Epistaxis.....	2
Sensitivity of skin.....	1

*Signs*

Chills or chilly sensations.....	32
(often accompanied by sweating)	
Râles.....	11
Fever without chills or sweating.....	10
Bronchial or bronchovesicular breathing.....	5
Conjunctivitis.....	5
Dullness on percussion.....	4
Increased vocal fremitus.....	4
Dyspnea.....	3
Cyanosis.....	2
Delirium.....	2
Rash.....	1
Incontinence.....	1
Decubitus ulcers.....	1

Generalized aching was a prominent complaint and was more pronounced in the lower extremities. Cough occurred in all the patients with pneumonitis. Five patients had frankly bloody sputum, which was not observed in previously reported cases.<sup>17</sup> There were no patients in the series who had "rusty" or "prune juice sputum."

The chest pain was described as substernal discomfort or burning or more severe pain on coughing or deep inspiration over the lower lateral chest wall.

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, or constipation were not infrequent. The only complaints of one patient without pneumonitis were nausea, vomiting, diarrhea, and a dull frontal headache. As in Derrick's cases,<sup>7</sup> burning of the eyes, lacrimation, and conjunctival injection were found in a few patients.

Physical signs of pneumonitis, such as dullness on percussion, râles, bronchial breathing, etc., were easily detected in most of the patients with pulmonary involvement. A few of the pneumonitis cases could not be differentiated clinically from lobar pneumonia. Bradycardia, although present in some cases, was not constant, and was thought to be of no value in differential diagnosis. The spleen was not palpable in any case.

Routine laboratory studies were not particularly helpful. Most of the patients on whom blood counts were obtained had a normal white blood cell count and differential, although one patient with evidence of pneumonitis had a count as high as 18,000 with 86 per cent neutrophils. In general, the sedimentation rate was moderately increased during the febrile course of the illness, but returned to normal when the patient recovered. Sputum smears and cultures showed staphylococci, *Streptococcus viridans*, or a few pneumococci that could not be typed. Albuminuria occurred in the patients who had high temperatures and cleared up after the temperature returned to normal.

Chest roentgen-rays in the pneumonitis cases were similar to those described by Hornibrook and Nelson.<sup>17</sup> In a few cases the consolidation observed was like that of lobar pneumonia; the changes in other cases could not be differentiated by roentgen-ray from those caused by atypical pneumonia. Electrocardiograms taken on one patient during the course of his illness and on six patients during their convalescence were normal.

Many patients complained of aching of the legs and thighs for variable periods after apparent recovery from the illness. A few continued to have this symptom as long as three months. Fatigue was another common complaint and lasted in a few cases as long as one month. One patient had an acute thrombophlebitis of the leg during convalescence from his illness. One patient was rehospitalized for a probable thrombophlebitis following her discharge from the hospital; however, further observation revealed no evidence of venous thrombosis.

Various diagnoses by various physicians were made in this group of patients before the true nature of the illness was recognized. In the milder cases the most common diagnosis was influenza. Without serological studies or animal inoculations it would be difficult to make a differential diagnosis between influenza of a mild type and less severe cases of Q fever. During the outbreak, illnesses occurred in the personnel of Building No. 5 which were clinically indistinguishable from serologically established cases of Q fever but which, on repeated tests, showed a negative reaction in the complement fixation test for Q fever. The incidence of these and other acute respiratory illnesses in Building No. 5 during the outbreak was found to be similar to that in a comparable group outside this building.<sup>1</sup> Because of the headaches, some patients were thought to have sinusitis. Two cases of malaria were thought at first to be Q fever because of the chills, fever, sweating, and headaches. One patient was treated for rheumatic fever at first, as her prominent symptoms were pains in the extremities. The diag-

nosis of typhus fever was considered in one case because of the macular rash which resembled that of typhus. In contrast to other rickettsial diseases such as Rocky Mountain spotted fever, scrub typhus, and epidemic typhus, relatively mild cases of Q fever were not unusual in the older age groups and despite two critical cases, there were no fatalities.

The diagnosis of Q fever was confirmed in all cases by the complement fixation test, using antigens prepared from the American and Italian strains of rickettsia. The technic employed in the test was described by Bengtson.<sup>20</sup> The Italian Q antigen was found to be the more sensitive. The highest serum titers with this antigen on specimens taken during or after the illness ranged from 1:16 to 1:4096. With the American Q antigen the titers ranged from 1:4 to 1:512. Organisms identified as *Rickettsia burneti* were isolated from the whole blood of five cases and from the sputum of one.<sup>2</sup> Four of 45 convalescent sera tested failed to react with the American antigen, though they reacted to the Italian antigen.

In general, the sera tested by complement fixation were negative until 10 to 14 days after the onset of the illness. In many of the patients the diagnosis of the illness was not established until clinical recovery had occurred. There was no correlation between the severity of the illness and the complement fixation titer. The highest titer for both the antigens was found in a patient who continued working throughout a mild attack of the illness (Case No. 9).

Other serological studies were done on many cases, including complement fixations for spotted fever, endemic typhus, and psittacosis, with negative results. Weil-Felix agglutinations with *Proteus* OXI9, OX2, and OXK were negative.

Penicillin and sulfadiazine were given to a majority of the patients having the more severe form of the illness, with the result that neither good nor ill effects were apparent. Three patients were given blood transfusions. Two of these received immune blood from donors who had the illness in the 1940 outbreak.<sup>17</sup> There appeared to be no definite improvement following this therapy. One patient was placed in an oxygen tent for about one week, which relieved his dyspnea. In general, the treatment was symptomatic and in the more severe cases supportive.

### CASE REPORTS

The following cases are reported as examples of patients with mild and severe forms of the illness and of patients with and without pneumonitis:

*Case 16:* A severe case with pneumonitis, white male, age 42. On February 11, 1946, the patient had sudden onset of chills and fever and nausea and vomiting. His symptoms continued and he was admitted to the hospital on February 14. On admission, his temperature was 104.6° F., pulse 120, and respirations 25. Soon after admission his temperature rose to 106° F. (figure 1). His face was flushed, his sensorium was clear, and there was no dyspnea nor cyanosis. The left side of the chest

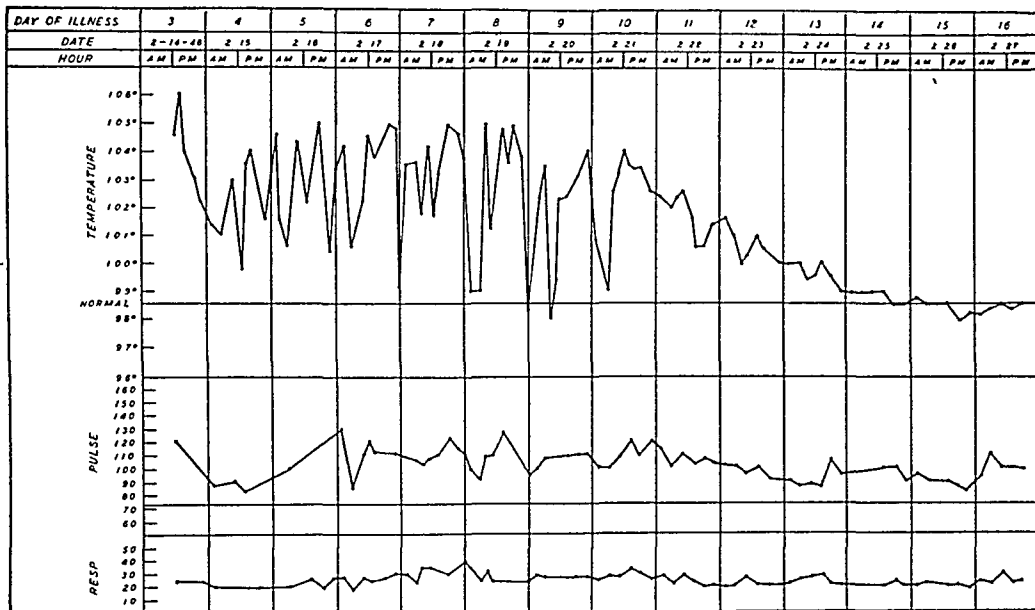


FIG. 1. Case 16.

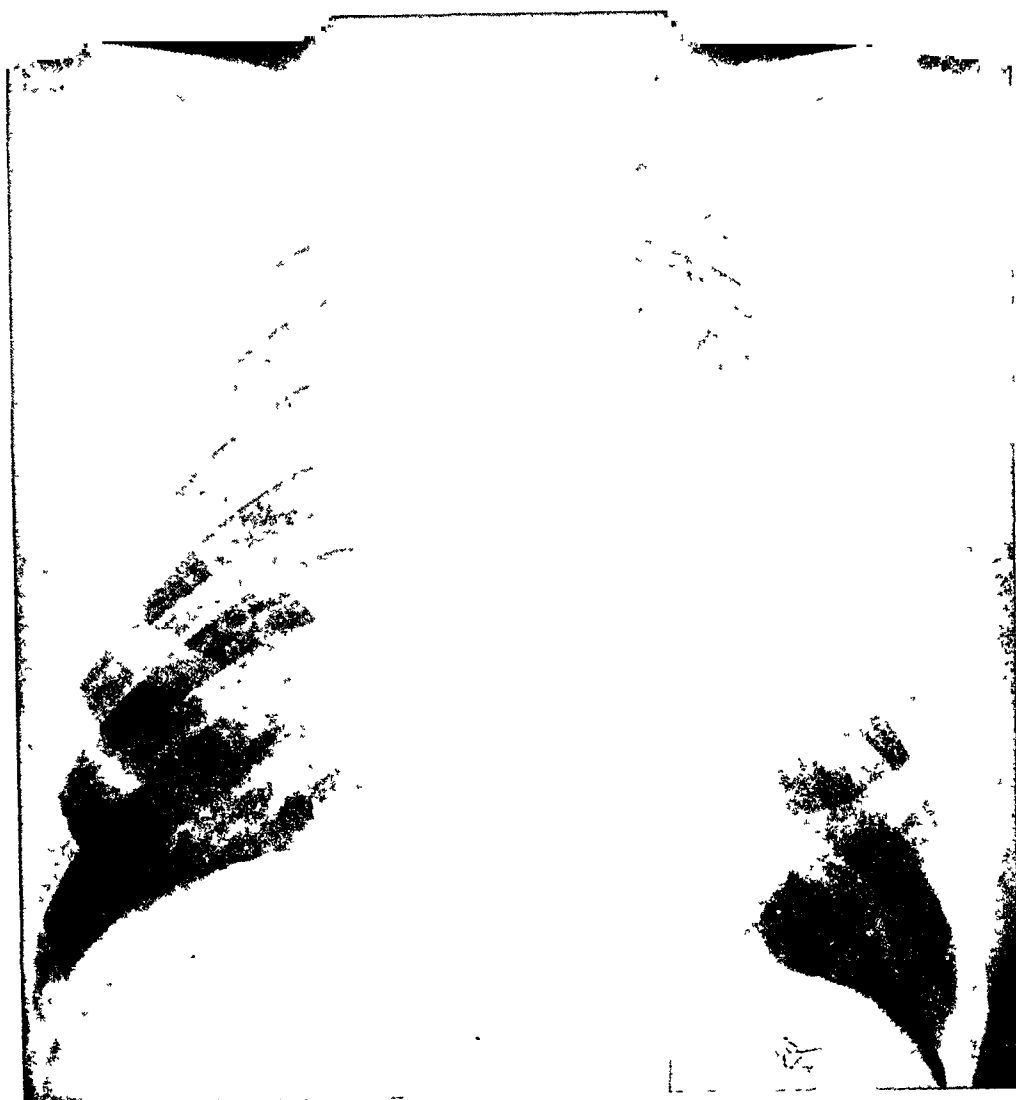


FIG. 2. Case 16.



showed decreased excursion and there were crepitant râles in the left mid-chest anteriorly. There was generalized abdominal tenderness. Roentgen-ray of the chest showed a heavy mottled consolidation in the lower portion of the left upper lobe (figure 2). The white blood cell count was 13,200 with 72 per cent neutrophiles, 25 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed 2 plus albumin and many coarsely granular casts. *Streptococcus viridans* and *Staphylococcus albus* were cultured from the sputum.



FIG. 3. Case 16.

The patient was started on penicillin, 20,000 units every three hours intramuscularly. He showed no response, however, and the penicillin was discontinued on February 19. He developed a cough after admission to the hospital and this gradually became worse until on February 18 he began to expectorate sputum containing bright red blood. About this time his respirations became somewhat rapid, but he did not complain of dyspnea. Examination of the chest at this time showed dullness, bronchial breathing, and râles over the left mid-chest.

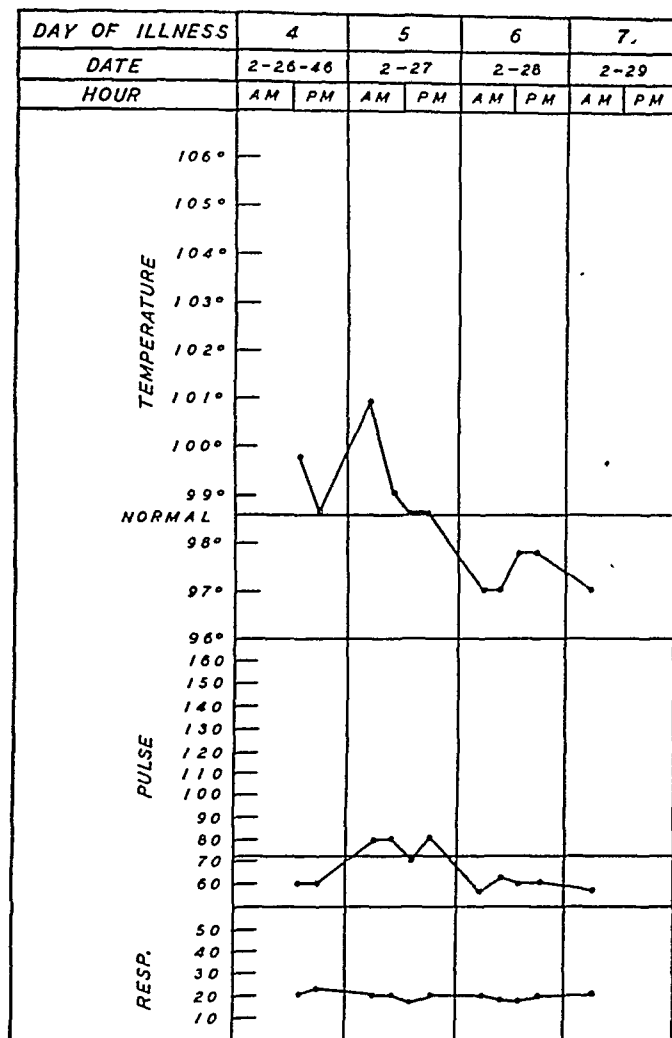


FIG. 4. Case 31.

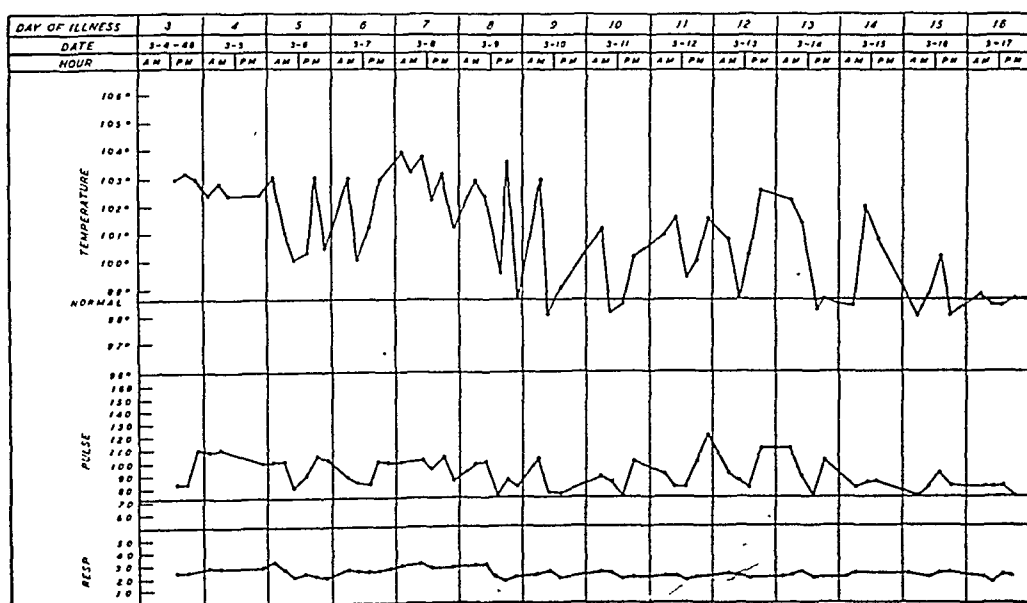


FIG. 5. Case 31.

Oxygen therapy with a tent was tried but the patient refused to stay in the tent. On February 19 his white cell count was 12,300 with 85 per cent neutrophils. On February 20 his icterus index was 8 and the non-protein nitrogen was 25 mg. per cent. On February 21 the serum albumin was 3.51, serum globulin 2.58, malaria smear negative, hemoglobin 74 per cent, red cell count 4,250,000 and white cell count 9,000 with 82 per cent neutrophils. The patient's condition continued to be poor. He had two severe episodes of epistaxis, was weak, and mentally clouded. He was given intravenous fluids, two transfusions, and sulfadiazine, one gram every four hours.

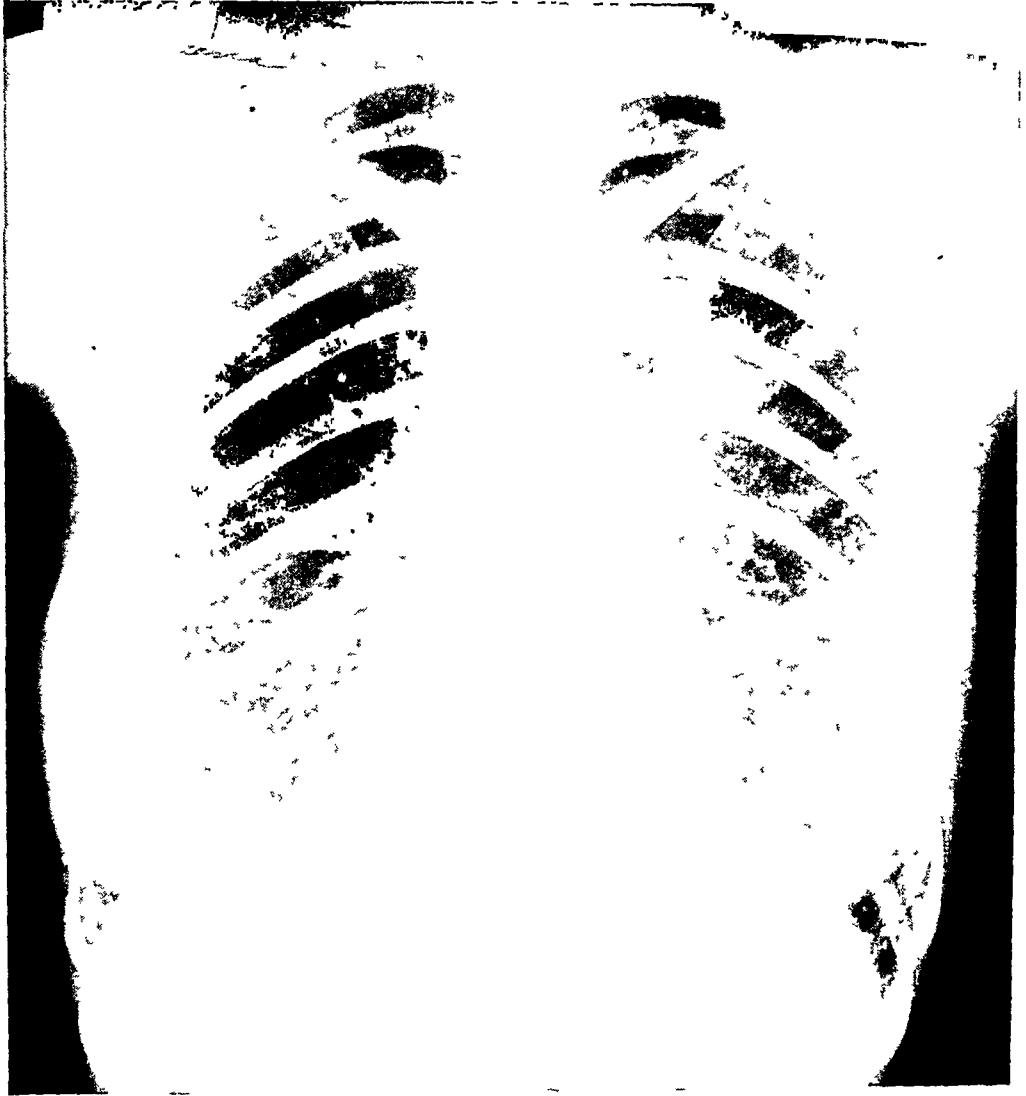


FIG. 6. Case 26.

The sulfadiazine was continued until the fifteenth day of illness, by which time the patient's fever had returned to normal by lysis and his cough had disappeared. He continued to have a rapid pulse. Electrocardiogram at this time was within normal limits except for tachycardia. At no time did the patient complain of headache. On March 3 acute thrombophlebitis of the left lower extremity developed. This complication responded very well to lumbar sympathetic injection. Roentgen-ray of the chest on March 19 showed scant mottling of the left mid-lung (figure 3).

On February 15 and February 19, the complement fixation test for Q fever was negative. On February 25, it was positive 1:512 with the American antigen, and greater than 1:512 with the Italian antigen.

*Case 23:* A mild case without pneumonitis, white male, age 29. On February 23 this patient complained of a malaise and anorexia. The evening of that day he had chills and fever, a severe frontal headache, and mild substernal pain; a slight cough developed later. On February 25 his afternoon temperature was 102° F. The next day he was admitted to the hospital. Physical examination was negative on

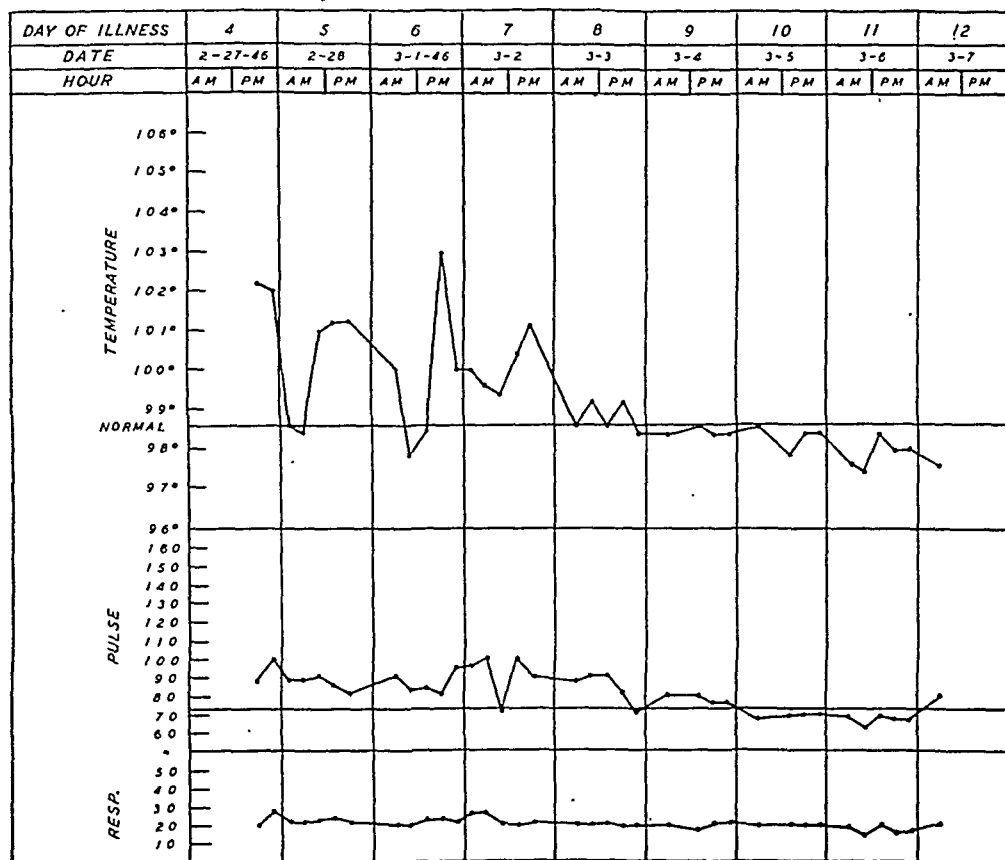


FIG. 7. Case 26.

admission except for a temperature of 99.8° F. (figure 4), and his symptoms had cleared up. Roentgen-ray of the chest was negative. On February 27 his white cell count was 5,500 with 74 per cent neutrophils, 24 per cent lymphocytes, and 2 per cent monocytes. On February 28 his temperature remained normal and on March 1 he was discharged from the hospital. On March 15 he returned to work but continued to complain of some fatigue until the latter part of March.

On February 28 complement fixation for Q fever was negative with both the Italian and American antigen. On March 6 his serum was positive 1:128 with the Italian antigen, and 1:16 with the American. On April 8 the titers were 1:16 with the Italian and 0 with the American antigen.

*Case 31:* A severe case without pneumonitis, white male, age 58. On March 1, 1946, this patient began to have anorexia, malaise and headache. On March 2 he had chills and fever and severe frontal and occipital headache. He was admitted to the

hospital on this date. He gave a history of a chronic cough with copious expectoration of mucopurulent sputum for years.

Physical examination on admission showed an acutely ill, drowsy patient whose temperature was 103° F., pulse 85, respirations 25. His chest was emphysematous and there were musical and crackling râles at both lung bases. Roentgen-ray of the chest showed generalized bronchitic changes and thickened pleura at both costophrenic angles. His sedimentation time was 16 mm. in one hour, hemoglobin 85 per cent,



FIG. 8. Case 9.

red cell count 5,100,000, white cell count 68,000 with 79 per cent neutrophils, 11 per cent lymphocytes, and 10 per cent monocytes. Urinalysis showed a specific gravity of 1.022 and was otherwise negative.

Throughout the course of his illness the patient complained of headache, substernal pain, and generalized aching. On March 9 he received a transfusion of immune blood without noticeable effect. His treatment was otherwise symptomatic.

Roentgen-ray of the chest on March 9 showed no change, and the patient continued to have a normal white cell count and normal urinalysis. On March 13 he was found to have skin lesions on his chest, abdomen, and arms. The lesions were dull red macules 2 to 5 millimeters in diameter and blanched on pressure. The rash resembled that of typhus and gradually faded until it had disappeared on March 19.

The patient continued to have fever until March 17 (figure 5). On May 13 he was still complaining of pains in the legs. On March 8 complement fixation with the Italian antigen was negative; on March 14 the titer was greater than 1:512. On April 10 his serum was positive with the Italian antigen in a titer of 1:256, and with the American, 1:512.

*Case 26:* A moderately severe case with pneumonitis, white female, age 33. On February 22 the patient had generalized aching, malaise, and headache. These symptoms continued until February 24 when she had chills, fever, and sweating. The following day she began to have rather severe pain in both lower extremities, burning of the eyes, and lacrimation. On February 27 she was admitted to the hospital. Physical examination on admission showed a rather drowsy patient whose temperature was 102.2° F., pulse 90, and respirations 20. There were no chest signs nor other findings. Roentgen-ray of the chest showed a small homogenous consolidation extending upward and outward from the left hilus. There were many fine discrete calcifications in both lungs (figure 6). The urinalysis was negative. The hemoglobin was 80 per cent, red cell count 4,450,000, white cell count 5,600 with 60 per cent neutrophils, 1 per cent eosinophiles, 1 per cent basophiles, 31 per cent lymphocytes, and 7 per cent monocytes.

The patient's symptoms and fever continued until March 3 (figure 7). Roentgen-ray of the chest on March 7 showed marked improvement and was negative except for calcifications on March 14. Treatment was symptomatic. She was discharged from the hospital on March 7 and was readmitted for probable thrombophlebitis on March 18. No evidence of this complication was found and she was discharged on March 25. She returned to work on April 8, but when last seen on May 12 was still complaining of pains in the lower extremities.

On March 5 the complement fixation titer with the Italian antigen was greater than 1:512, and with the American, 1:256. On April 8 both gave titers of 1:128.

*Case 9:* A mild case without pneumonitis, white male, age 60. On February 8 this patient had sudden onset of vomiting and diarrhea and a dull frontal headache. Following this he felt as though he had a fever for two or three days. He continued working, however. Roentgen-ray of the chest on March 18 showed some increase in the lung markings but was otherwise negative (figure 8). He complained of a headache until March 8.

On February 18 complement fixation with the Italian antigen was negative. On February 28 and March 28 the titer was 1:1,024 with the same antigen. The titer with the American antigen on February 28 was 1:128.

### SUMMARY

1. Forty-five of 47 cases of Q fever occurring during a laboratory outbreak were studied from a clinical standpoint.

2. Pneumonitis was not the predominant clinical characteristic of this outbreak, although it was shown to be present in 13 of the cases.

3. In many of the pneumonitis cases the lung lesions were easily found by physical signs. Bloody sputum was observed in five of these patients.

4. Mild cases occurred. The difficulties in making a differential diagnosis are pointed out. In this respect the value of a sensitive and accurate

method of making a diagnosis, such as is provided by the use of the Italian antigen in serological tests, is apparent.

5. Penicillin, sulfadiazine, and transfusions of immune blood were found to have no definite effect on the course of the disease.

#### BIBLIOGRAPHY

1. HUEBNER, R. J.: Report of an outbreak of Q fever at the National Institute of Health. II. Epidemiological features. (To be published.)
2. HUEBNER, R. J., and duBUY, HERMAN: Report of an outbreak of Q fever at the National Institute of Health. III. Laboratory and certain experimental epidemiological features. (To be published.)
3. IRONS, J. V., TOPPING, N. H., SHEPARD, C. C., and COX, H. R.: Outbreak of Q fever in the United States, Pub. Health Rep., 1946, lxi, 784-785.
4. ROBBINS, F. C., and RAGAN, C. A.: Q fever in the Mediterranean area: Report of its occurrence in American troops. I. Clinical features of the disease, Am. Jr. Hyg., 1946, xlv, 6-22.
5. Commission on Acute Respiratory Diseases. Identification and characteristics of the Balkan grippé strain of *Rickettsia burneti*, Am. Jr. Hyg., 1946, xlv, 110-122.
6. CHENEY, G., and GEIB, W. A.: The identification of Q fever in Panama, Am. Jr. Hyg., 1946, xlv, 158-172.
7. DERRICK, E. H.: Q fever, a new fever entity: clinical features, diagnosis and laboratory investigation, Med. Jr. Australia, 1937, ii, 281-289.
8. DERRICK, E. H.: *Rickettsia burneti*, the cause of Q fever, Med. Jr. Australia, 1939, i, 14.
9. DAVIS, G. E., and COX, H. R.: A filter-passing infectious agent isolated from ticks: isolation from *Dermacentor andersoni*, reaction in animals and filtration experiments, Pub. Health Rep., 1938, liii, 2259.
10. COX, H. R.: A filter-passing infectious agent isolated from ticks: description of organism and cultivation experiments, Pub. Health Rep., 1938, liii, 2270.
11. COX, H. R.: Studies of a filter-passing infectious agent isolated from ticks: further attempts at cultivation on cell-free media: suggested classification, Pub. Health Rep., 1939, liv, 1822.
12. COX, H. R.: *Rickettsia diaporica* and American Q fever, Am. Jr. Trop. Med., 1940, xx, 463.
13. DYER, R. E.: A filter-passing infectious agent isolated from human ticks. IV. Human infection, Pub. Health Rep., 1938, liii, 2277.
14. BURNET, F. M., and FREEMAN, M. A.: A comparative study of rickettsial strains from an infection of ticks in Montana and from Q fever, Med. Jr. Australia, 1939, ii, 887.
15. DYER, R. E.: Similarity of Australian Q fever and a disease caused by an infectious agent isolated from ticks in Montana, Pub. Health Rep., 1939, liv, 1229.
16. BURNET, F. M., and FREEMAN, M. A.: Note on a series of laboratory infections with the rickettsia of Q fever, Med. Jr. Australia, 1939, i, 11-12.
17. HORNIBROOK, J. W., and NELSON, K. R.: An institutional outbreak of pneumonitis. Epidemiological and clinical studies, Pub. Health Rep., 1940, lv, 1936.
18. DYER, R. E., TOPPING, N. H., and BENGTON, I. A.: An institutional outbreak of pneumonitis, isolation and identification of causal organism, Pub. Health Rep., 1940, lv, 1946.
19. LILLIE, R. D., PERRIN, T. L., and ARMSTRONG, C.: An institutional outbreak of pneumonitis. Histopathology in man and rhesus monkeys in the pneumonitis due to the virus of Q fever, Public Health Rep., 1941, lvi, 149-155.
20. BENGTON, I. A.: Complement fixation in rickettsial diseases. Technique of test, Pub. Health Rep., 1944, lix, 402-405.

# THE CLINICAL SIGNIFICANCE OF DIVERTICULOSIS, INCLUDING DIVERTICULITIS, OF THE GASTROINTESTINAL TRACT\*

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THE frequency of diverticula in various portions of the gastrointestinal tract necessitates a careful interpretation of their significance, symptoms and treatment. They may occur with no symptoms whatsoever, or they may be solely responsible for the complaints of the patient. At times their differentiation from neoplasm and other serious organic conditions may be most difficult.

Diverticula are blind sacs with small necks lined by mucosa and opening into the gastrointestinal tract. The exact nature of their pathogenesis is not completely understood. As a rule they seem to result from congenital weakness of the wall, or from inability of the muscular layers to withstand the intraluminal pressure to which they are constantly subjected. Diverticula are found in all portions of the digestive tract—most commonly in the colon, not infrequently in the esophagus, stomach, duodenum and small intestine. The first descriptions were those of Sommering in 1794 and Cruveilhier in 1849.<sup>1</sup>

## ESOPHAGUS

In a monograph on diseases of the esophagus, Zenker and Ziemssen in 1877 classified esophageal diverticula into the pulsion and traction types—a classification in practical use today.<sup>2</sup> The pulsion type occurs at the lower portion of the pharynx and is, thus, frequently referred to as the pharyngo-esophageal, or Zenker's diverticulum. The so-called traction diverticulum most frequently develops in the region of the left main bronchus or near the cardia.

## PULSION DIVERTICULA

The pharyngo-esophageal diverticulum is a true herniation of the mucosa and sub-mucosa through the fibers of the inferior constrictor muscles of the pharynx as they run transversely or through the obliquely dividing fibers of the cricopharyngeus muscles on the posterior aspect of the esophagus. As these muscles spread off to become longitudinal and envelope the esophagus, they leave on the posterior wall an area weakly supported by muscularis. In the course of many years, the intraluminal pressure produces the formation of a diverticulum (figure 1).

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The symptoms are directly referable to the act of swallowing. Careful inquiry usually reveals that the dysphagia is first noticed with dry foods. It increases gradually in magnitude until finally water and other liquids are regurgitated. In two of our cases the obstruction was so marked that a loss of weight of 20 and 40 pounds respectively developed within a few months.

There is a definite relationship between the symptoms and the size of the sac.<sup>3</sup> During the earliest stages there is simply a projection of the mucosa and sub-mucosa through the fibers of the crico-pharyngeus muscle and no

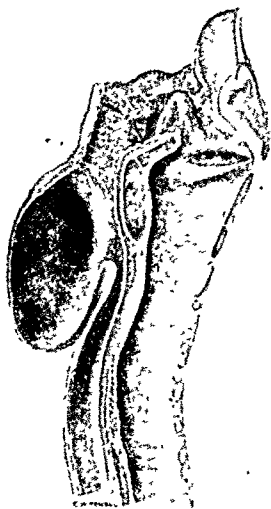


FIG. 1.—Pulsion diverticulum, sagittal section showing diverticulum, pouch, diverticulum, and esophagus. (Royal College of Surgeons Museum)

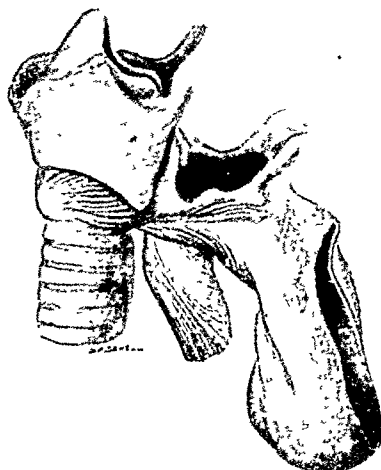


FIG. 2.—Dissection showing laryngopharyngeal diverticulum with fibers of crico-pharyngeus muscle in its mouth and lower fibers of esophagus in its neck. (Royal College of Surgeons Museum)

FIG. 1. Pulsion diverticulum (from Abel<sup>7</sup>).

sac is actually present. Dry particles of food may lodge in this projection. When a small sac actually forms there is then a regurgitation of mucus with food eaten previously. Eating and swallowing are frequently associated with gurgling which becomes particularly bothersome to the patient. When the sac enlarges, descends into the mediastinum and causes an angulation of the esophagus obstructive symptoms ensue.

In diagnosis the history is far more important than the physical examination: Roentgen-ray demonstrates the diverticulum easily. Esophagoscopy is seldom necessary. The following case is illustrative:

L. T., a 54 year old female, complained of difficulty in swallowing and of a choking sensation in the chest for two years. There had been some nausea and vomiting during this period. The patient stated that the dysphagia was noted with solid food only at first and that by massaging the throat the food could be made to pass. The dysphagia became progressively worse and by the time she was seen in the clinic, considerable trouble was encountered in swallowing liquids. The physical

and laboratory examinations were normal. Roentgenography revealed a large pharyngo-esophageal diverticulum. The sac was excised by two-stage operation with complete symptomatic relief (figure 2, left).

Nicolodoni, in 1877, has been credited with the first operation, although Wheeler is said to have performed the first successful one.<sup>2</sup> In all of the surgically treated cases reviewed by us recovery has been uneventful and with complete relief of the symptoms. The two-stage operation appears to



FIG. 2. (left) Pulsion diverticulum of the pharynx. (right) Traction diverticulum of the esophagus.

be the procedure of choice. The mortality rate is lower and there is less danger of mediastinitis. In 1939 Lahey<sup>3</sup> reported 104 such operations with only one death.

### TRACTION DIVERTICULA

Of 20 traction diverticula selected at random from the clinic files 10 were located in the mid-portion of the esophagus near the bifurcation of the trachea and 10 near the cardia. In seven of the 20, the presenting symptoms were fairly typical of the associated organic disease: cholelithiasis 2, gastric ulcer 2, duodenal ulcer 1, and carcinoma of the stomach and pleural effusion each 1. In five of these the symptoms subsided after institution of therapy

for the organic condition; the other two came to the clinic for diagnosis only and hence were not followed. In eight cases the diverticula represented accidental findings in patients with functional bowel distress; the symptoms subsided with appropriate therapy. In the remaining five cases there was no evidence of a co-existing disease. The symptoms referable to the esophagus were substernal burning, discomfort after eating and intermittent dysphagia. In each instance the symptoms improved with reassurance, the use of a bland diet, and the prescription of belladonna and phenobarbital. Some recurrence of symptoms was noted in one or two patients but not in the others. Symptoms such as these are seen quite frequently in patients without esophageal diverticula and without other organic disease. We have not been able to associate traction diverticula with any definite symptomatology. The following cases are illustrative:

E. W., a 65 year old female, complained of nervousness, cramps in the arms and legs, and headaches of indefinite duration. There were no esophageal symptoms. The physical examination was essentially normal. The traction diverticulum noted roentgenologically in the lower esophagus was considered of no clinical significance (figure 2, right).

A. K., a 53 year old male, entered the hospital on July 16, 1941, complaining of a period of gnawing epigastric pain of seven years' duration. The pain was of the ulcer type occurring approximately two hours after meals. He also mentioned the fact that for many years there had been some difficulty in swallowing his food completely. The physical examination disclosed tenderness in mid-epigastrium. The maximum gastric acidity (histamine) was 116. Roentgen-ray revealed a pyloric ulcer with deformity of the antrum and spectacular esophageal diverticula (figure 3). At operation on July 21, 1941, a duodenal ulcer was found for which a posterior gastroenterostomy was performed. Recovery was uneventful and the patient was discharged with instructions to continue medical ulcer management. He has remained free of symptoms and has not experienced any significant difficulty in swallowing.

There are autopsy records of traction diverticula associated with such complications as mediastinal abscess, bronchial fistula and pulmonary gangrene. Moersch and Finney<sup>6</sup> in a review of 39 cases of esophago-tracheo-bronchial fistula found two (5 per cent) arising from a traction diverticulum in the middle third of the esophagus near the tracheal bifurcation. These must be considered as rarities not of much significance in the routine practice of medicine.

#### GASTRIC DIVERTICULA

Gastric diverticula are also thought to arise either from pulsion or traction. About 65 per cent of them occur near the cardia.<sup>8</sup> In a large series of stomachs examined roentgenologically by Reich,<sup>8</sup> diverticula were found in less than one half of 1 per cent. Martin<sup>9</sup> analyzed 103 uncomplicated cases of pulsion diverticula; 63 were located in the cardia, 11 in the mid-portion and 14 in the prepyloric area along the lesser curvature; nine occurred along the greater curvature; five in the mid-portion and four in the prepyloric area; six were miscellaneous.

The roentgenologic detection of diverticula of the upper end of the stomach may be difficult and require careful search in various positions.<sup>10</sup> Gastrosocopy may confirm the diagnosis and aid in the differentiation of diverticulum-like formation occurring secondary to perforating peptic ulcer or carcinoma<sup>11</sup>; in the typical lesion at the cardia gastroscopy gives very little information and may even be dangerous.

G. D., a 43 year old female, complained of nausea, burning epigastric pain and constipation for one year. The symptoms had appeared following the death of her mother from cancer and persisted through the illness of her son with rheumatic fever.

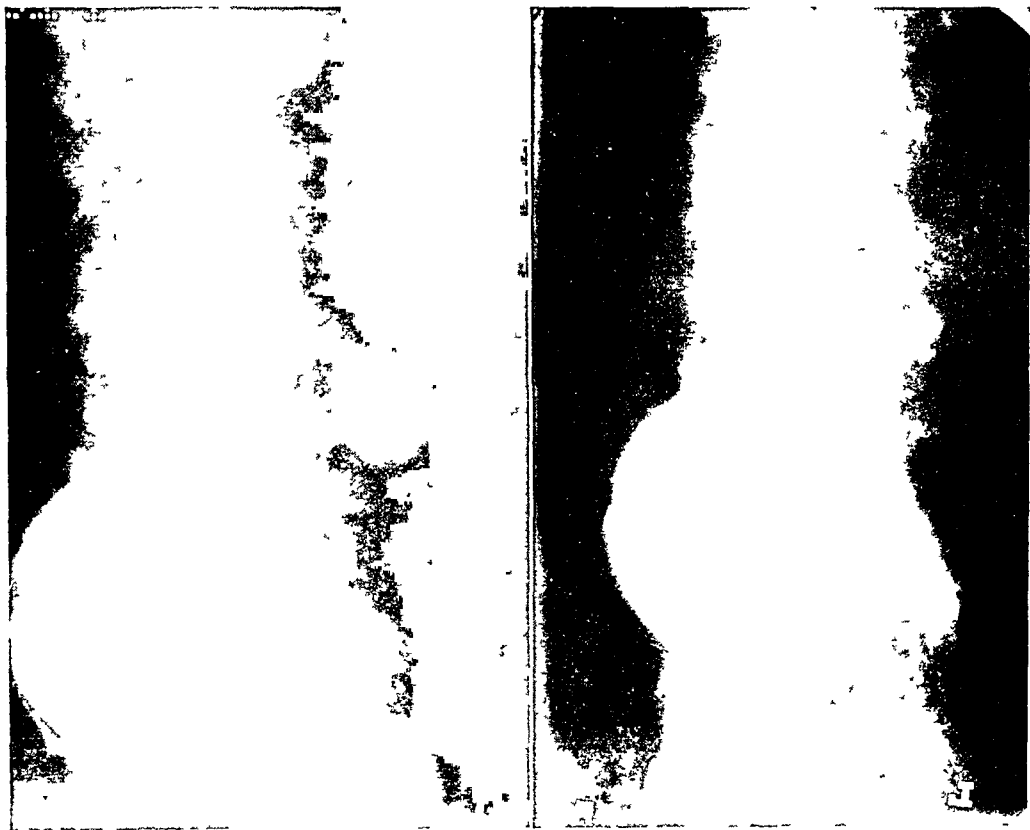


FIG. 3 Multiple traction diverticula of the esophagus.

Roentgenograms were reported to have disclosed either a diverticulum or an ulcer near the cardia. The roentgenologist was said to have advised immediate operation; the local physician prescribed a bland diet with antacids. The patient experienced some relief, but she was confused by the conflicting advice and continued to worry about her condition. Our examination elicited the above information and disclosed a normal physical and laboratory examination except for the demonstration of a histamine-fast achlorhydria. The presence of a gastric diverticulum was established roentgenologically (figure 4). The nature of the lesion was explained to the patient in detail with firm reassurance. The constipation was treated with a diet and antispasmodics. Marked improvement ensued. The patient's own conclusions were as follows: "I think I overworked, worrying about my son, my husband, and my mother dying of cancer. I built up a complete anxiety neurosis without intending

to do so and then I went to the doctor. The x-ray man found the diverticulum and advised me to have an immediate operation. The doctor treated me and I worried."

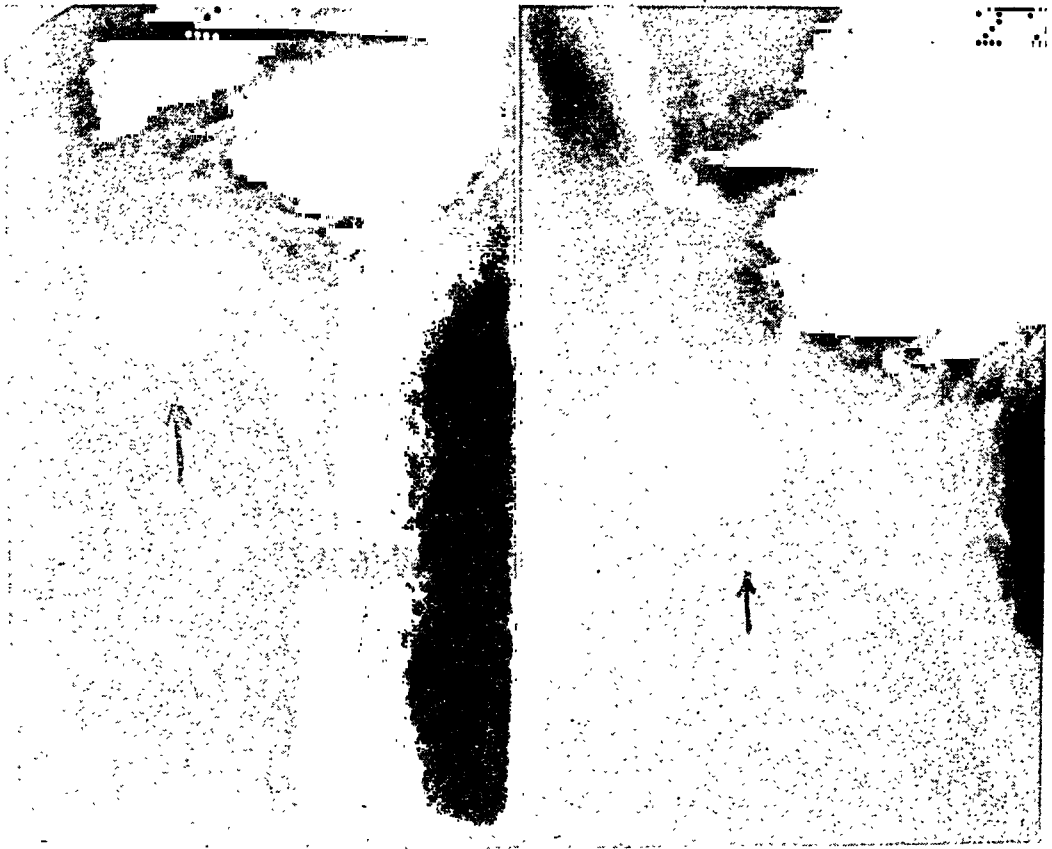


FIG. 4. Gastric diverticulum.

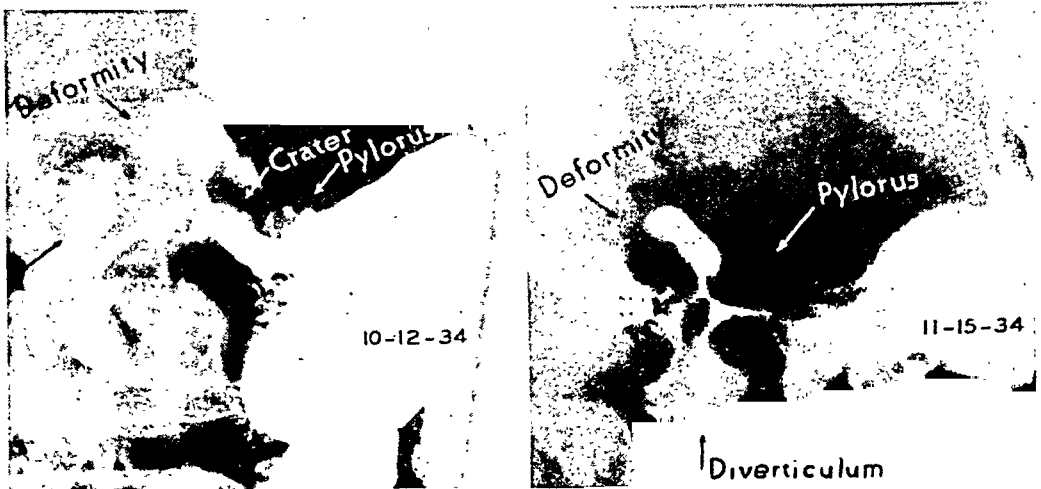


FIG. 5. Duodenal ulcer with crater (left hand view) and bilateral contracture of a large bulb with resultant pseudodiverticula formation proximal to the deformity.

## DUODENAL DIVERTICULAE

Priority in the description of duodenal diverticula has been erroneously credited to Morgagni (1765) and to Sommering (1794). The first case was described by Chomel in 1710.<sup>13</sup> The pouch was apparently secondary to a cholecysto-duodenal fistula, for it contained "twenty-two stones of yellow color with smooth polished surfaces." These lesions were then looked upon as surgical curiosities. Virchow, Grases, and Fisher during the latter part of the last century gave accurate anatomic descriptions, and the papers of W. J. Mayo, Beer, Moynihan, Drummond, Mummery and others brought out their clinical significance.<sup>14</sup> Since the publications of Odgera (1929) and Edwards (1935), duodenal diverticula have generally been classified as primary or congenital, and those secondary to duodenal ulcer. Some authors have listed vaterine diverticula as a special type because of the sequelae occasionally seen.

One of the chief problems in connection with duodenal diverticula is the differentiation of the congenital diverticulum and the pseudodiverticulum produced by a chronic ulcer with much scarring. Congenital diverticula are very rare in the first portion of the duodenum, the duodenal bulb, whereas almost all of the ulcer diverticula occur in this area.

A. B., a 40 year old male giving a history of a periodic epigastric distress of the ulcer type of 10 years' duration, was found on roentgen-ray examination (figure 5) to have a high-grade deformity of the duodenal bulb with crater formation and two pseudodiverticula formed by the scarring from the ulcer. After the crater of the ulcer had disappeared or become very much smaller the deformity of course persisted as did the pockets on either side of the bulb between the pylorus and the deformity—the classical pseudodiverticula produced by the hour glass contracture of the bulb. The gastric free acidity (Ewald) was 45.

Lesions at the apex of the bulb may be either diverticula or ulcer; indeed the differentiation may be impossible until response to treatment has been observed.

A 47 year old male, A. C., was seen because of burning and pressure beneath the sternum for three weeks. The patient had been treated for 12 years for chondrosarcoma of the left iliac bone. The burning discomfort appeared in the afternoon, late evening and occasionally about 4 or 5 a.m. It was never present in the forenoon. The maximum gastric free acidity (histamine) was 108 clinical units. A roentgen-ray examination revealed a collection of barium interpreted as a diverticulum of the second portion of the duodenum (figure 6). The distress was completely relieved by ulcer management. A second roentgen-ray study three weeks later disclosed a marked decrease in the size of the presumed diverticulum; a third examination some weeks later showed its complete disappearance and thus proved that the original lesion had in fact been a peptic ulcer.

For all practical purposes neoplastic ulceration does not need to be considered in the differential diagnosis of lesions in the bulb but it does require consideration in those of the second, third and fourth portions. The roent-

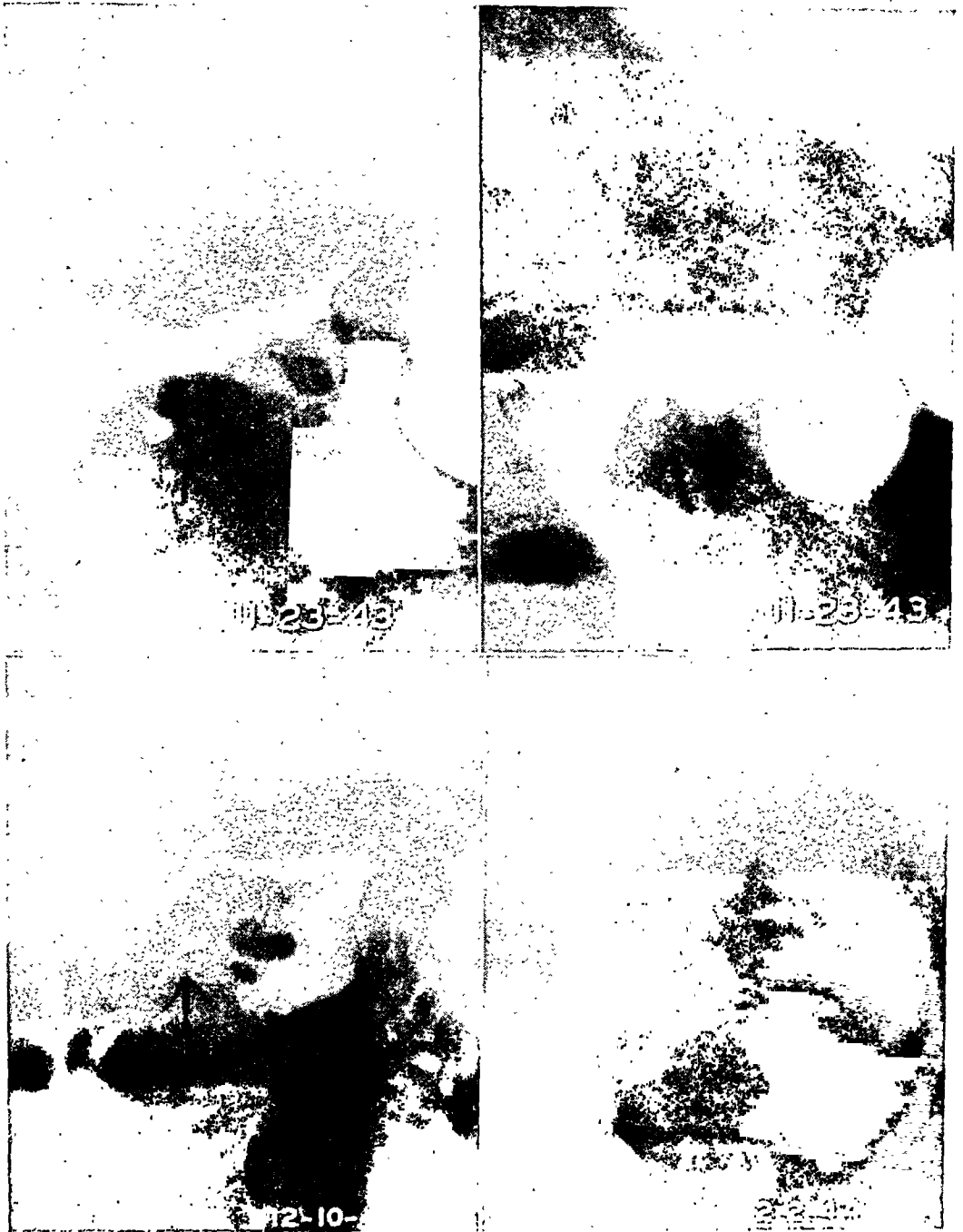


FIG. 6. Duodenal ulcer simulating diverticulum of the second portion of the duodenum.  
The crater disappeared on ulcer management.

genologic manifestations are usually clear cut and are associated with loss of appetite, loss of weight and occult blood in the feces.

In our experience it has rarely been necessary to pay any attention to duodenal diverticula. The symptoms are usually due to organic disease elsewhere, such as duodenal ulcer or cholelithiasis, or to a functional dis-

turbance. Relief is obtained with appropriate therapy and without regard to the diverticula.

S. B., a 55 year old male, had been perfectly well except for three attacks of typical biliary colic. Roentgen-ray disclosed a faint visualization of the gall-bladder with two diverticula of the second portion of the duodenum (figure 7). At operation



FIG. 7. Multiple diverticula second portion of duodenum

a gall-bladder containing both sand and stones was found and removed. The symptoms were relieved.

In three of our cases of duodenal diverticula obstructive manifestations were present; resection of the lesion gave complete relief of the symptoms in two; the third experienced a stormy postoperative period and died.



G. G., a 57 year old male, complained of umbilical pains appearing several hours after meals and relieved by milk and food. For the past year he had experienced nausea and vomiting four to 10 times weekly. There had been a weight loss of 12 pounds in the last six months. The only significant finding during physical examination was tenderness about the umbilicus. The urinalysis and blood count were normal. Gastroduodenal roentgenograms revealed a large diverticulum in the third portion of the duodenum (figure 8). Laparotomy on November 9, 1944, confirmed the roentgenographic findings; the diverticulum was excised. Postoperative recovery was complicated by right lower lobe pneumonia. At the time of discharge the patient was completely relieved of his digestive symptoms.

Another rare complication of duodenal diverticula is obstruction of the pancreatic ducts with pancreatic necrosis. Ogilvie in 1941 collected four

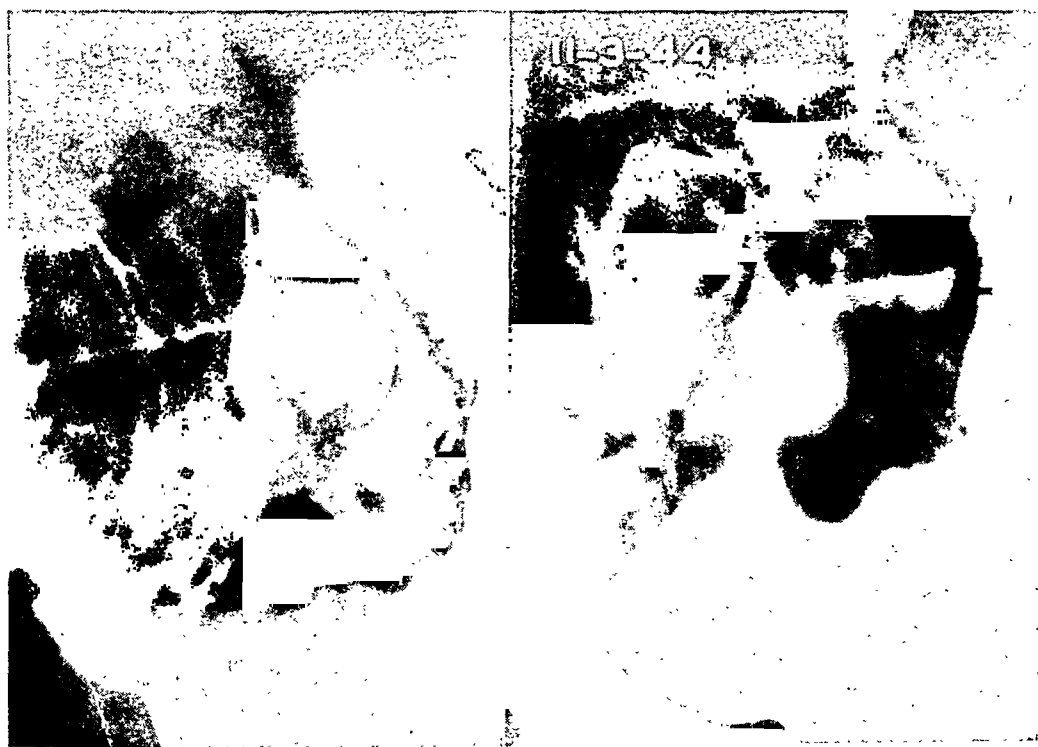


FIG. 8. Diverticulum of the third portion of the duodenum. On the left, faint outline of bulb, diverticulum filled above and to the right. In right hand view, bulb filled with barium, diverticulum with gas (fluid level present).

such cases. In three of these, the pancreatic ducts were described as dilated.

Duodenal diverticula rarely become inflamed, probably because of three factors: (1) the sterility of their contents, (2) their retro-peritoneal position, and (3) their inverted position and wide ostia.<sup>12</sup> On the other hand the ostium is often concealed among the plicae circulares of the duodenum and the wall of the sac contains little or no muscle. Case found that while the average emptying time of the sac in 18 consecutive cases was 11 hours, barium was not uncommonly retained beyond 48 hours and in one case for seven days. Such retention is not a serious matter and does not warrant operation.

Basset (1907), Rosenthal (1908) and Bauer (1912) apparently reported the first cases of acute diverticulitis of the duodenum.<sup>12</sup> Perforation is a rare sequela; Beaver<sup>19</sup> described an instance in 1938 and found in the English literature only three other cases. Boland<sup>22</sup> stressed the fact that the symptoms simulate perforated peptic ulcer and urged that if the operation reveals nothing more than an exudate along the anterior duodenal wall an incision should be made in the posterior peritoneum to search for a perforated diverticulum. Peri-diverticulitis is also a rare sequela.<sup>24</sup>

In spite of the fact that Chomel in 1710 in describing the first diverticulum recorded the presence of gall stones within it, enteroliths are nevertheless uncommon. Harris<sup>20</sup> (1932) during an operation on a 49 year old female discovered a peri-vaterine diverticulum containing a large, annular stone consisting mainly of cholesterol.

Apparently the only reported instance of carcinoma in association with a duodenal diverticulum is described by Morrison and Feldman.<sup>27</sup>

The advisability of surgical treatment in most duodenal diverticula is highly questionable.<sup>21</sup> Complications such as hemorrhage and diverticulitis are very rare. Operation is usually technically rather difficult and extensive. It is much wiser to try a medical regimen based on a conservative diet and the use of antispasmodics, reserving operation for the exceedingly small group of patients with definite and persistent inflammation. Pain and tenderness are not in themselves conclusive evidence of diverticulitis, for other conditions such as a duodenal ulcer or a tender colon may account for these manifestations.

### JEJUNUM

Diverticula are found less frequently in the jejunum than in any other portion of the gastrointestinal tract. Case<sup>24</sup> in reviewing the literature from 1854 to 1920 was able to collect only 17 non-Meckelian diverticula in either the jejunum or ileum at operation or necropsy. However by 1938 the number had increased to 187.<sup>25</sup> In only 12 of these was there acute inflammation or perforation. Diverticula may occur in any portion of the circumference of the bowel, but most of them are located near the mesentery or between the leaves of the mesentery. They may be multiple or single, large or small. They are usually discovered accidentally at operation, autopsy or by roentgen-ray. When uncomplicated they are rarely if ever responsible for the patient's symptoms and require no treatment. The complications of non-Meckelian diverticula of the small bowel are similar to those of Meckel's diverticula although much more rare.<sup>26</sup> Treatment is indicated for the complications only, primarily intestinal obstruction or acute diverticulitis.<sup>27</sup>

### MECKEL'S DIVERTICULUM

Meckel's diverticulum occurs as a result of incomplete obliteration of the omphalo-mesenteric duct, its structure depending on the degree of obliteration. The diverticulum is usually situated on the anti-mesenteric side of

the ileum, 30 to 90 cm. proximal to the ileo-cecal valve. In rare instances it may occur at any point between the stomach and the colon.<sup>28</sup> It may be attached to other viscera, or to the abdominal wall; rarely it is located between the leaves of the mesentery.<sup>29</sup> The size of the opening into the ileum is important because when the opening is wide it permits the unhindered entrance and exit of intestinal contents. However, this wide neck may also permit the lodgement of a large variety of foreign bodies. The incidence of Meckel's diverticulum is 1.5 to 3 per cent of all persons, the frequency being twice as great in males as in females.<sup>28</sup>

The symptoms depend primarily on the nature of the complication present, obstruction and inflammation being the most frequent ones in adults, peptic ulcer with hemorrhage the most common one found in children. The acute catarrhal, phlegmonous, and gangrenous forms of diverticulitis occur, complicated by perforation with abscess formation or peritonitis. The symptoms are so similar to those of acute appendicitis that the diagnosis is rarely made prior to operation although a peri-umbilical location of the pain and tenderness is suggestive of diverticulitis. The treatment is, of course, operation with surgical removal.

The frequency with which Meckel's diverticula are the cause of intestinal obstruction is rather surprising. Miller and Wallace found 63 instances of intussusception in 201 cases of Meckel's diverticula found at operation. Harkins<sup>36</sup> found such diverticula to be responsible for 2 per cent of all cases of intussusception. Intestinal obstruction may also result from adhesions about a diverticulum.

Peptic ulcer is the most frequent complication of Meckel's diverticulum.<sup>30, 32, 33</sup> The presenting symptom in 81 per cent of such cases is intestinal hemorrhage.<sup>32</sup> The bleeding is often profuse and persistent. The pathogenesis of these ulcers has been clearly established pathologically and experimentally. They are found only in diverticula containing ectopic gastric mucosa the incidence of which has been estimated as 16 per cent.<sup>29</sup> There have been numerous theories to explain the presence of these aberrant elements, the most commonly accepted one being that of Albrecht who maintains that the entodermal lining of the primitive intestinal tube possesses the potentiality of developing into any of the glandular components of the fully developed gastrointestinal tract.<sup>28</sup> The ectopic gastric mucosa contains acid and pepsin secreting glands; the presence of acid secretion has been demonstrated.

J. W., a 17 year old male, complained of intermittent pain in the abdomen and *marked muscular weakness for three years*. The pain was described as a knife-like sticking sensation in the region of the umbilicus somewhat to the left of the mid-line. Pain was most apt to occur from one half to three quarters of an hour after the noon and evening meals. Physical examination revealed marked pallor and a palpable spleen. Laboratory examinations revealed a profound secondary anemia and the persistent presence of occult blood in stools. Prior to operation two blood transfusions of 500 c.c. each were given. Following the second transfusion, the patient

suddenly developed symptoms suggesting an internal hemorrhage and later passed a stool containing a large amount of liquid and clotted blood. At operation an inflammatory mass was found in the ileum about 40 cm. from the cecum. A section of ileum, approximately 60 cm. in length, containing the mass was resected. The resected ileum contained a Meckel's diverticulum about 4 cm. in length and completely surrounded by an inflammatory mass (figure 9, top). Near the entrance of the



FIG. 9. (above) Longitudinal section of Meckel's diverticulum lined with gastric mucosa and surrounded by jejunal mucosa—reduced from magnification  $10\times$  (kindness Dr. Lester Dragstedt). (below) Gastric ulcer at the mouth of Meckel's diverticulum—reduced from magnification  $20\times$  (kindness Dr. Lester Dragstedt).

diverticulum was a round perforated ulcer approximately 1.5 cm. in diameter (figure 9, bottom). Histologic examination disclosed gastric mucosa lining the entire diverticulum (figure 10). The ulcer had penetrated the mucosa, sub-mucosa and muscularis and produced a marked inflammation in the serosa.



FIG. 10. Gastric mucosa lining Meckel's diverticulum—reduced from magnification 125 $\times$  (kindness Dr. Lester Dragstedt).

Dragstedt and Matthews have produced similar lesions experimentally by allowing the acid gastric juice from a Pavlov pouch to drain into a blind loop of small intestine.

A malignant tumor of Meckel's diverticulum is rare enough to be called a pathological curiosity.<sup>35</sup> Nygard and Walters<sup>35</sup> in 1937 made a survey of 20, six carcinomas and 14 sarcomas. In one of these an adenocarcinoma had developed in heterotopic gastric mucosa.

### COLON

Diverticula of the colon, as in all other parts of the digestive tract, have been classified as true or false, congenital or acquired. Congenital true diverticula involving all layers of the intestinal wall are seen occasionally but the vast majority of colonic diverticula are formed by the herniation of the mucosa through the muscular layers.<sup>38</sup> Neither autopsy nor roentgen-ray studies have given as yet the true incidence in the various age groups.<sup>39, 37, 40</sup> The term diverticulosis denotes simply the presence of diverticula. Clinical manifestations appear only when secondary inflammation develops,<sup>41</sup> diverticulitis. Diverticulitis seems to be caused chiefly by fecalith obstruction of the neck which prevents adequate drainage and leads to pressure necrosis.<sup>37</sup> The inflammation may progress until the mucous membrane within the diverticulum undergoes atrophy with subsequent round cell infiltration of the submucosa followed by ulceration and perforation.<sup>37</sup> Extension of the process can result in chronic thickening of the wall.

The symptoms of diverticulitis of colon are variable. There may be a single acute attack of pain, usually in the left lower quadrant lasting from one or two days to several days or even longer depending upon the complications present. There may be several such recurring attacks.

Brown and Marckley<sup>42</sup> reported that during the period from 1919 to 1929 in the Mayo Clinic, 277 cases of diverticulitis of the colon were treated medically; 99 (26 per cent) were subjected to operation at some time or other. The following case demonstrates the manner in which sufficient progress may be obtained under medical management.

C. W., a 63 year old female, complained for three weeks of acute attacks of lower abdominal cramp-like pain. Stools were of normal shape and color. Physical and laboratory examinations were normal. Roentgen-ray revealed diverticulosis and chronic diverticulitis of the sigmoid (figure 11, right). Treatment consisted of mineral oil and a bland diet. For the past four years the patient has gotten along very well although she has experienced transitory abdominal discomfort from time to time.

Usually the differentiation between diverticulitis and carcinoma is easy; it is difficult in a few cases, and occasionally it is almost impossible.<sup>42</sup> Diverticulitis may produce a stony-hard fixed mass quite indistinguishable on rectal examination from inoperable carcinoma. Carcinoma, like diverticulosis, is most commonly found in the sigmoid or descending colon. There is no satisfactory evidence that diverticulosis is a precursor of cancer.<sup>42</sup> The daily passage of gross red blood per rectum is always suggestive of carcinoma although it may result from hemorrhoids alone or from non-specific ulcera-

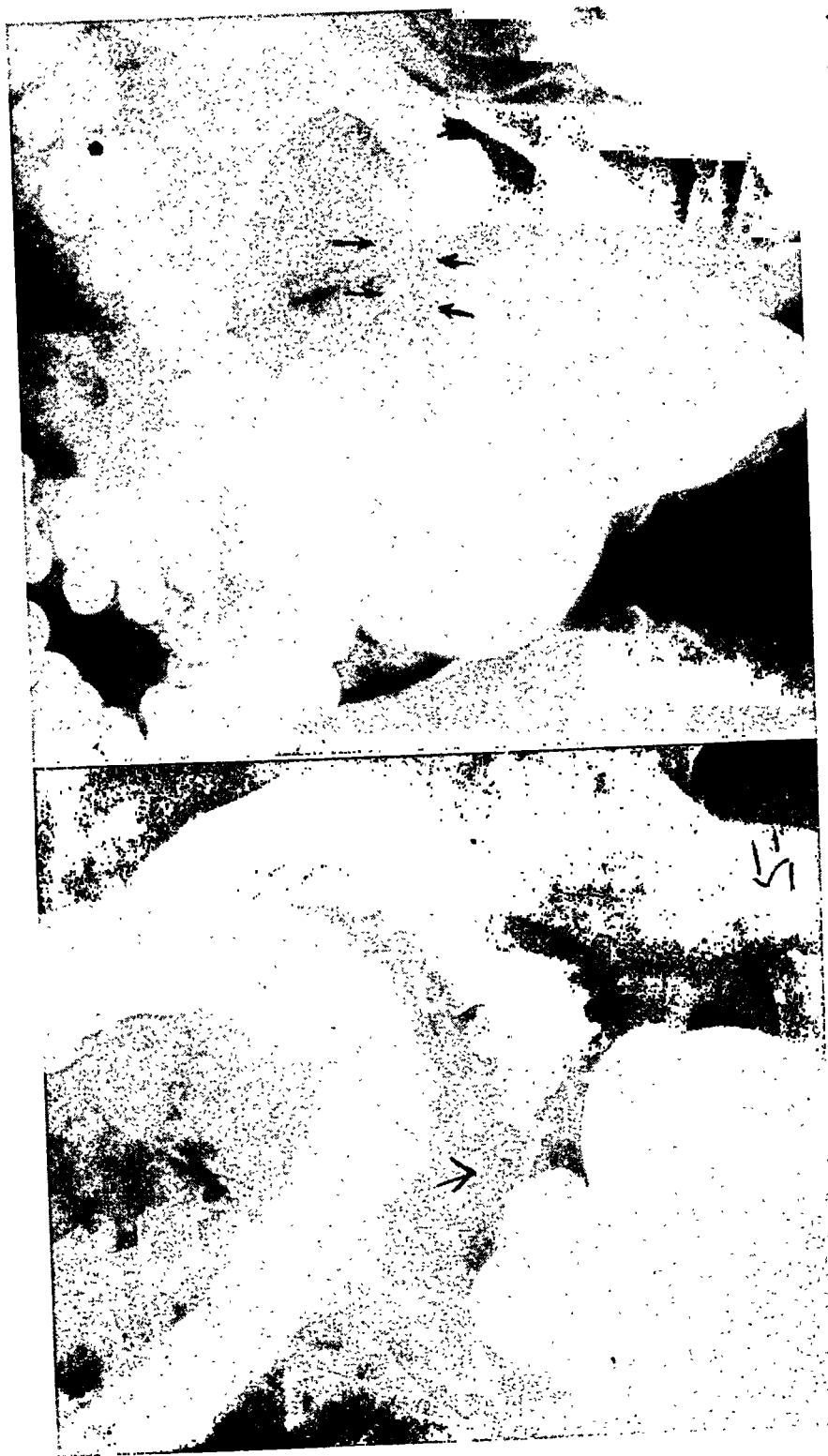


FIG. 11. Chronic diverticulitis of sigmoid responding satisfactorily to medical management (four years). (right) Chronic diverticulitis simulating carcinoma of the sigmoid.

tive colitis; in our experience rarely if ever is bleeding to be attributed to diverticulosis or to diverticulitis. The roentgenologic differential diagnosis depends on the fact that carcinoma tends to destroy the mucosa and to produce a margin in which no mucosal pattern can be seen whereas in diverticulitis the mucosal patterns persist and are usually exaggerated.

The following cases are illustrative of the difficulty in differentiation and also of some of the indications for surgical therapy.

L. S., a 47 year old female, complained of three attacks of "stoppage of the bowels" in the two years prior to admission. During each of these attacks she had been unable to move the bowels except with strong laxatives; enemas had been unsuccessful. Blood in the stools had been noticed. There had been no loss of weight or appetite. The physical examination revealed tenderness over the colon and a tender, non-movable mass at the junction of the rectosigmoid. Laboratory studies were normal. Roentgenograms revealed an irregular narrowing with partial obstruction of the recto-sigmoid, presumably carcinomatous (figure 11, left). No diverticula were noted. The lesion was resected and found to be a chronic diverticulitis with obstruction.

E. H., a 57 year old male, was first seen in March, 1940, complaining of fatigue, loss of appetite, and epigastric bloating for six months. Roentgen-ray disclosed diverticula and a "saw-tooth" deformity of the lower sigmoid with some narrowing of the lumen (figure 12, top). A low residue, non-laxative diet and antispasmodics were prescribed. The patient progressed very well until June, 1941, when he began to experience pain in the rectum on defecation. The stools were of small caliber, with no blood. Rectal examination disclosed a stony-hard fixed tender mass at the level of the rectosigmoid. Roentgenologically an obstructive deformity was demonstrated in this area with diverticula and evidence suggestive of a walled off perforation. A month later the mass was unchanged and the roentgen-ray deformity looked suspiciously like that of carcinoma (figure 12, bottom). Colostomy was performed in August 1941. The rectal mass decreased slowly in size and finally disappeared although the roentgenologic deformity persisted (figure 13, top). Resection of the lesion in June 1943, proved it to be chronic diverticulitis. The patient has remained well.

B. B., a 56 year old female, complained of weakness, anorexia, and lower abdominal pain for six to eight months. She had not had a bowel movement for seven days prior to admission. During the last two months she had had several gross hemorrhages from the bowel. Physical examination revealed mild abdominal distention; a questionable mass was palpated in the rectum. Laboratory studies disclosed a secondary anemia. Roentgen-ray revealed innumerable diverticula of the colon (figure 13, bottom) with an obstructive lesion of the rectosigmoid. On proctoscopic examination a carcinoma was found as proved by biopsy and by subsequent operation at which time an inoperable tumor was demonstrated.

Diverticula confined to the cecum alone are unusual. Noon and Schenk<sup>43</sup> in 1944, reported three cases of solitary diverticula of the cecum, reviewed the literature and found that up to that time 48 cases had appeared in the American and British literature. The condition was usually diagnosed preoperatively as appendicitis and at the operating table frequently as carcinoma of the cecum. They concluded that minimal surgery should be done because of the tendency of diverticulitis to subside spontaneously. Diverti-



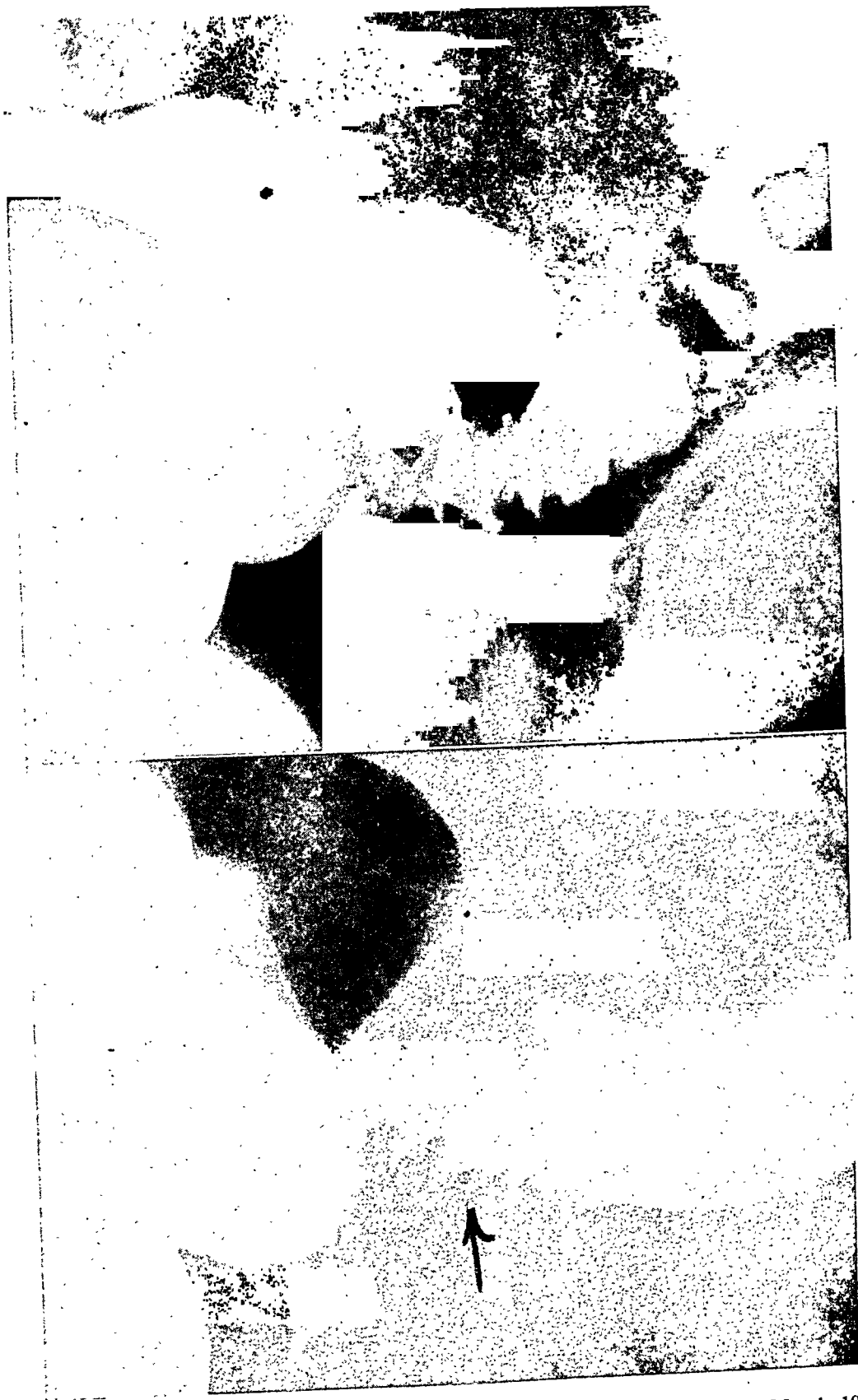


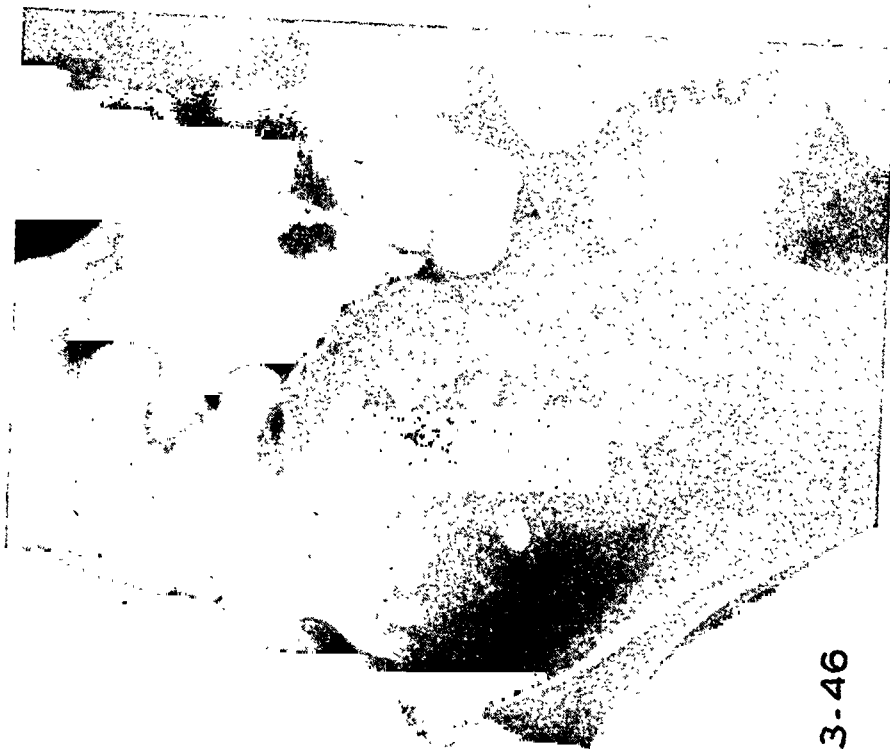
FIG. 12. Chronic diverticulitis of sigmoid with obstruction increasing from March 1940 (top) to August 1941, simulating carcinoma.



FIG 13. (top) Persistence of obstructive lesion 21 months after colostomy. (bottom) Extreme diverticulosis of descending colon and sigmoid obscuring carcinoma of recto-sigmoid, demonstrated by roentgen-ray and proctoscopy.



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FIG. 14. Diverticulosis of the cecum.

culectomy or inversion of a solitary diverticulum may be indicated in rare instances.<sup>44</sup> The following case is illustrative:

B. M., a 45 year old female, complained of right lower quadrant abdominal distress and gurgling for one month. The distress apparently had no relationship to food; it was relieved by the passage of flatus. Physical examination revealed slight generalized tenderness over abdomen. The laboratory examinations were normal including six stools negative for occult blood by the benzidine test. Roentgen-ray revealed diverticulosis of cecum (figure 14). The patient was reassured; a diet was outlined; antispasmodic drugs were prescribed. Marked improvement has occurred, but the patient still notices some rather localized tenderness and at times discomfort.

### CONCLUSIONS

Diverticula of the digestive tract, particularly of the colon, are extremely common; the esophagus and duodenum are quite frequently affected; the stomach and jejunum rarely so. Uncomplicated diverticula do not as a rule produce symptoms. An exception is to be found in the pulsion diverticulum of the pharynx in which symptoms may arise early merely from the lodging of food in the "dimple" or in the later stages from the obstruction and kinking of the esophagus produced by the distended sac. Diverticula of the esophagus proper, of the stomach, duodenum and small intestine rarely become inflamed except for the Meckel's diverticula. Diverticulitis of the small bowel simulates acute appendicitis. Diverticula may produce intestinal obstruction from intussusception or from adhesions. Peptic ulcer of Meckel's diverticulum, manifested usually by hemorrhage, is a rather common lesion in children. Diverticulitis of the rectosigmoid ordinarily subsides without surgical interference; in some instances resection is indicated. The differentiation between diverticulitis and carcinoma is at times difficult.

### BIBLIOGRAPHY

1. WALLACE, R. P.: Traction diverticula of the esophagus, *Med. Clin. N. Am.*, 1942, xxvi, 889-894.
2. MAHLE, A. E., and CHRISTOPHER, FREDERICK: Esophageal diverticulum, *Illinois Med. Jr.*, 1942, lxxxii, 124-128.
3. LAHEY, F. H.: Esophageal diverticula, *Arch. Surg.*, 1940, xli, 1118-1140.
4. LAHEY, F. H.: The management of pulsion esophageal diverticulum, *Jr. Am. Med. Assoc.*, 1937, cix, 1414-1419.
5. LAHEY, F. H.: Two stage removal of pulsion esophageal diverticulum, *Surg. Clin. N. Am.*, 1939, xix, 591.
6. MOERSCH, H. J., and FINNEY, W. S.: Fistula between esophagus and tracheobronchial tree, *Med. Clin. N. Am.*, 1944, xxviii, 1001-1007.
7. ABEL, A. L.: Esophageal obstruction, its pathology, diagnosis and treatment, 1929, Humphrey Milford Oxford University Press, p. 69, 102.
8. REICH, N. E.: Diverticula of the stomach, *Am. Jr. Digest. Dis.*, 1941, viii, 70-76.
9. MARTIN, L.: Gastric diverticula, *Ann. Int. Med.*, 1936, x, 447-465.
10. REINEKE, H. G.: Diverticula of upper end of stomach, *Am. Jr. Roentgenol.*, 1941, xlii, 650-654.

11. SCHMIDT, H. W., and WALTERS, W.: Diverticula of the stomach, *Am. Jr. Surg.*, 1941, liii, 315-318.
12. OGILVIE, R. F.: Duodenal diverticula and their complications with particular reference to acute pancreatic necrosis, *Brit. Jr. Surg.*, 1940-41, xxviii, 362-379.
13. KELLOGG, E. L.: The duodenum, 1933, Paul B. Hoeber, Inc., New York, page 221.
14. BUTLER, P. F., and RITVO, M.: Diverticulum of the duodenum, *Boston Med. and Surg. Jr.*, 1925, cxcii, 705-712.
15. LAHEY, F. H.: Surgery of duodenum, *New Eng. Jr. Med.*, 1940, ccxxii, 444-450.
16. MONSARRAT, K. W.: Acute perforation of a duodenal diverticulum, *Brit. Jr. Surg.*, 1926-27, xiv, 179.
17. HUDDY, G. P. B.: Duodenal diverticula with report of a case of gangrenous diverticulitis *Lancet*, 1923, ii, 327-330.
18. LUCINIAN, J. H.: Diverticulum of duodenum perforated into the pancreas, *Am. Jr. Roentgenol. and Radium Therapy*, 1930, ccxxiv, 684.
19. BEAVER, J. L.: Acute perforation of a duodenal diverticulum, *Ann. Surg.*, 1938, cviii, 153-154.
20. HARRIS, V. C. J.: Diverticulum of the duodenum associated with calculous formation, *Brit. Med. Jr.*, 1932, i, 1080.
21. FINNEY, J. M. T.: Duodenal diverticula, their significance and treatment, *South. Surg.*, 1942, xi, 543-554.
22. BOLAND, F. K.: Acute perforated duodenal diverticulum, *Surgery*, 1939, vi, 65-67.
23. KOZINN, P. J., and JENNINGS, K. G.: Jejunal diverticulitis, *Am. Jr. Dis. Child.*, 1941, lxii, 620-623.
24. CASE, J. T.: Diverticula of the small intestine other than Meckel's diverticulum, *Jr. Am. Med. Assoc.*, 1920, lxxv, 1463-1470.
25. GERSTER, J. C. A.: Diverticula of jejunum, *Ann. Surg.*, 1938, cvii, 783-800.
26. OWENS, G. H. C.: Acute diverticulitis of jejunum, *Brit. Jr. Surg.*, 1942-43, xxx, 239-240.
27. BENSEN, RAYMOND, DIXON, C. F., and WAUGH, J. M.: Non-Meckelian diverticula of jejunum and ileum, *Ann. Surg.*, 1943, cxviii, 377-393.
28. ABRAHAM, SERVETNICH, and NICHOLS, H. G.: Hemorrhage from Meckel's diverticulum in an adult, *New Eng. Jr. Med.*, 1943, ccxxviii, 12-14.
29. ABT, J. A., and STRAUSS, A. A.: Meckel's diverticulum as a cause of intestinal hemorrhage, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 991-996.
30. COBB, D. B.: Meckel's diverticulum with peptic ulcer, *Ann. Surg.*, 1936, ciii, 747-768.
31. MASON, J. M., and GRAHAM, G. S.: Ulceration of aberrant gastric mucosa in Meckel's diverticulum, *Ann. Surg.*, 1932, xcvi, 893-910.
32. MATT, J. G., and TIMPON, P. J.: Peptic ulcer of Meckel's diverticulum, case report and review of literature, *Am. Jr. Surg.*, 1940, xlvii, 612-622.
33. ABRAHAM, SERVETNICH, and NICHOLS, H. G.: Hemorrhage from Meckel's diverticulum in an adult, *New Eng. Jr. Med.*, 1943, ccxxviii, 12-14.
34. DRAGSTEDT, L. R.: Ulcus acidum of Meckel's diverticulum, *Jr. Am. Med. Assoc.*, 1933, ci, 20-22.
35. NYGAARD, K. K., and WALTERS, W.: Malignant tumors of Meckel's diverticulum, *Arch. Surg.*, 1937, xxxv, 1159-1172.
36. HARKINS, H. N.: Intussusception due to invaginated Meckel's diverticulum, report of two cases with study of 160 cases collected from literature, *Ann. Surg.*, 1933, xcvi, 1070-1095.
37. BEARSE, C.: Diverticulitis and diverticulosis of colon with special reference to patients under 40, *Rev. Gastroenterol.*, 1940, vii, 318-321.
38. BUIE, L. A.: Diverticula of the colon, *New Eng. Jr. Med.*, 1939, ccxxi, 593-598.
39. Vital Statistics, Special Reports (Summary of the United States Registration Area, 1936) Dept. of Commerce, Bureau of Census, 1938, iv, 957-958.
40. MAYO, W. J.: Diverticula of the sigmoid, *Ann. Surg.*, 1930, xcii, 739-743.

41. ARNHEIM, E. E.: Diverticulitis of colon with special reference to surgical complications, *Ann. Surg.*, 1940, cxii, 352-369.
42. BROWN, P. W., and MARCLEY, D. M.: Prognosis of diverticulosis and diverticulitis of colon, *Jr. Am. Med. Assoc.*, 1937, cix, 1328-1333.
43. NOON, Z. B., and SCHENK, H. L.: Solitary diverticulitis of the cecum, *Am. Jr. Surg.*, 1945, lxxviii, 364-368.
44. HENDTLASS, R. F.: Perforated solitary diverticulum of the cecum, *Brit. Med. Jr.*, 1941, ii, 309-310.

# FOUR IMPORTANT CONGENITAL CARDIAC CONDITIONS CAUSING CYANOSIS TO BE DIFFERENTIATED FROM THE TETRALOGY OF FALLOT: TRICUSPID ATRESIA, EISENMENGER'S COMPLEX, TRANSPOSITION OF THE GREAT VESSELS, AND A SINGLE VENTRICLE\*.

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*Boston, Massachusetts*

TODAY surgery holds much hope for the congenitally cyanotic patient in whom there is a diminution of blood flow to the lungs. Foreknowledge of the existing cardiac condition, of the position of the great vessels, and of any hidden congenital vascular anomaly would favor greatly a successful post-operative result.

Recent surgical advances in the treatment of the Tetralogy of Fallot reflect the importance both of the differential diagnosis and of the careful selection of suitable operative candidates. It is the purpose of this report to present four cases of cyanosis encountered at the Massachusetts General Hospital in which the final diagnosis was at variance with that of the Tetralogy of Fallot. In each of these cases clinical determination of the cardiovascular anomaly preoperatively would have been of great help to the surgeon, who followed in each instance the Blalock procedure, which consists of anastomosing a suitable vessel of the systemic arterial circulation to the pulmonary artery. We shall place special emphasis on a case of the rare tricuspid atresia, because it is coupled with a symptom complex which should differentiate it from other members of its category. In order to facilitate a more complete understanding of the material we are presenting, each case will be followed by a discussion. The four cases include (1) tricuspid atresia, (2) Eisenmenger's complex, (3) transposition of the great vessels, and (4) a single ventricle. Figure 1 illustrates the course of circulation in these four conditions.

## *Case 1. Tricuspid Atresia.*

T. S., a five and one half month old boy of American parentage, was admitted to the Massachusetts General Hospital on July 25, 1945, with the complaint of periodic attacks of persistent cyanosis over an interval of two and one half months. The patient was born at full term by normal delivery; no anesthetic was required. His birth weight was 10 pounds, two and one half ounces. The prenatal course was normal except for maternal vomiting throughout. The infant was bottle-fed from

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birth, many formulas having been tried before a satisfactory combination was found which resulted in a gain in weight. There were no illnesses of any kind until he reached three months of age. His parents then noted that during and after crying spells he presented a coughing type of respiration. During these episodes he would turn blue and become limp and would not regain his normal color until one or more hours later. After having been studied at a local hospital where roentgen-rays revealed the thymus to be enlarged, the child was given a course of deep roentgen-ray therapy in the hope of offsetting these cyanotic periods. However, this was of no avail and the patient was transferred to this hospital for study.

Both father and mother were living and well. One sibling, a four year old brother, had undergone a fusion operation of the spine for tuberculosis.

On physical examination the child's temperature was 99.8, pulse 130, respirations 36, and blood pressure 108 mm. of Hg systolic and 40 mm. diastolic. He was a normally developed, thin infant of a dusky slate blue color, active and aware of his surroundings. The scalp veins were markedly dilated and distended. Examination of eyes, ears, nose, throat, and neck was normal.

Examination of the heart revealed the left border of percussion dullness 1 cm. to the left of the midclavicular line, indicating slight enlargement. The point of maximal impulse was not apparent. Heart sounds were distinct: the rate was rapid and regular. There was a loud (Grade 4) \* systolic murmur, best heard in the second and third interspaces just to the left of the midsternal line. No thrill was palpable.  $P_2$  was greater than  $A_2$ .

Examination of the abdomen was negative. Reflexes were absent. The extremities showed slight clubbing of the fingers; the entire distal phalanges were blue.

Laboratory studies revealed essentially normal urinalyses except for an occasional blood cell. The red cell count ranged between 7 and 10 million cells per centimeter, and the white blood count ranged between 13 and 14,000 cells per centimeter. Hemoglobin values were between 13 and 16 grams and hematocrit between 40.8 and 73. A Hinton test was negative, as were skin tuberculin test and two blood cultures. The oxygen capacity of arterial blood was 2.7 volumes per cubic centimeter, the oxygen capacity of venous blood 22.6 volumes per cubic centimeter.

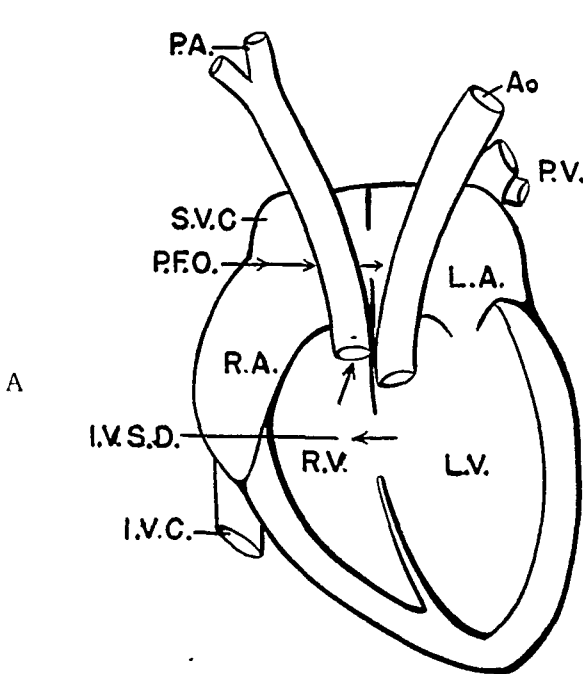
Fluoroscopy of the chest revealed the heart enlarged in the region of the left ventricle. There was no evidence of a right-sided aorta. Barium-swallowing function showed no definite abnormality or deformity of the esophagus suggestive of a vascular anomaly. On full roentgen-ray study of the chest the diaphragm was low in position. The costophrenic angles were clear and the lung fields were bright without definite evidence of parenchymal disease. These findings were strongly suggestive of congenital heart disease (figure 2).

An electrocardiogram (figure 3) showed sinus tachycardia at a rate of 150. The P-R interval measured 0.12 second. There was left axis deviation at an angle of  $-23^\circ$ . The T waves were slightly upright in Lead I, definitely upright in Lead II. The precordial leads were normal, with inversion of T in  $CF_2$  and prominent S waves in  $CF_{4,5}$ . Subsequent tracings showed no change. The finding of significance in this electrocardiogram is, then, the left axis deviation.

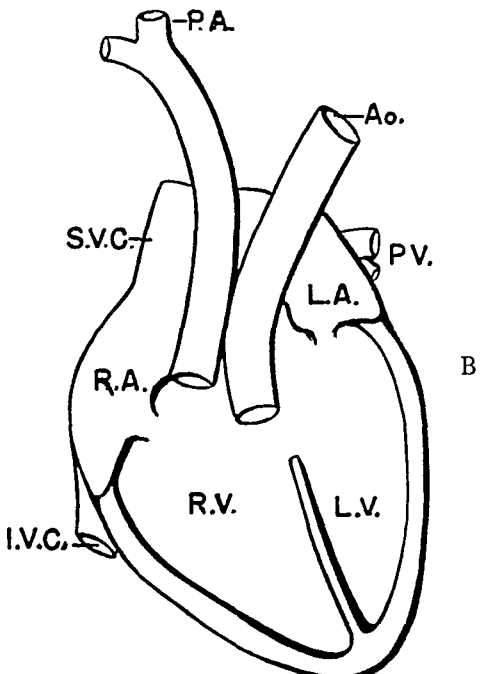
During his hospitalization the patient remained a diagnostic problem as regards the specific cardiac anomaly. He ran an afebrile course with variable respiratory and pulse rates. The number of cyanotic attacks was also variable, sometimes amounting to two or three, sometimes to five or six, a day. These were definitely associated with effort and seemingly were aided very little by oxygen. During these episodes it was noted that the murmur, which was easily audible under ordinary circumstances, disappeared.

\* Levine's classification of heart murmurs according to intensity: Grade 1 (faintest murmur audible on most careful auscultation) very slight; Grade 2 slight; Grade 3 moderate; Grade 4 loud; Grade 5 very loud; Grade 6 (loudest murmur one ever hears) loudest.

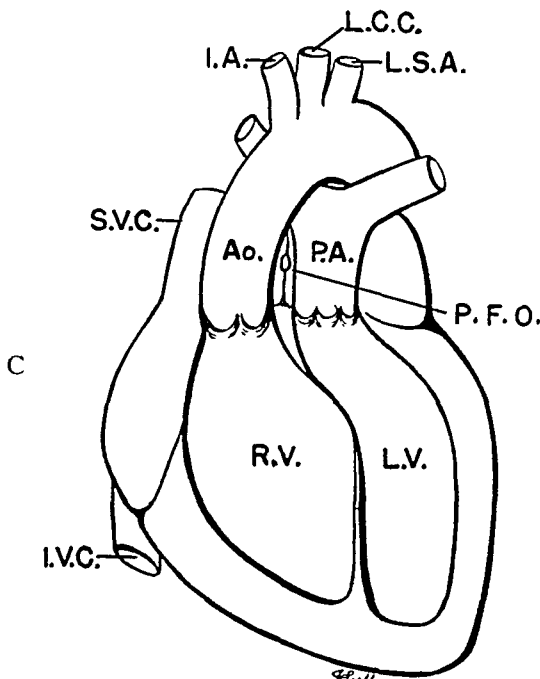




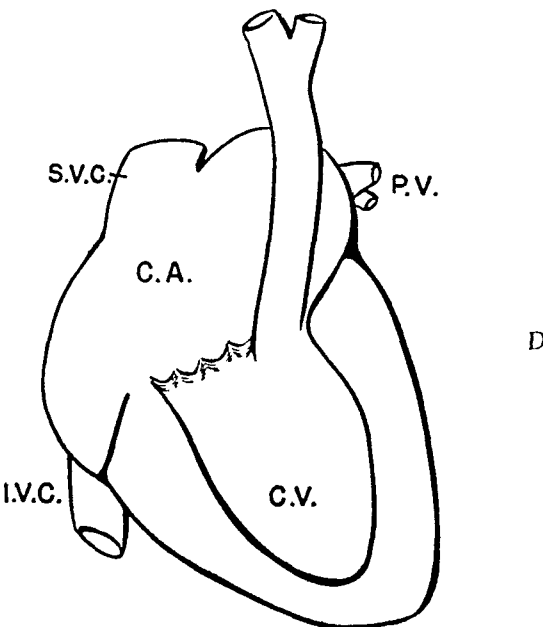
CASE 1.



CASE 2.



CASE 3.



CASE 4.

On July 30, 1945, digitalis was started because of newly developed dependent edema and increase in the intensity of the murmur. The patient was given 3 mg. of lanatoside-C (Cedilanid) intravenously, followed thereafter by 10 mg. of the powdered digitalis daily. The pulse continued at about 120. During the cyanotic spells the respiratory rate reached 60 to 65 with a slight concomitant rise in the pulse. It was thought that the loud systolic murmur at the basal area and the left axis deviation by electrocardiogram were consistent with the diagnosis of aortic or subaortic stenosis, but the cyanosis and polycythemia pointed to a right to left shunt, such as usually is found in the Tetralogy of Fallot or in a common arterial trunk. At all times the child retained the slate-gray appearance of his skin.

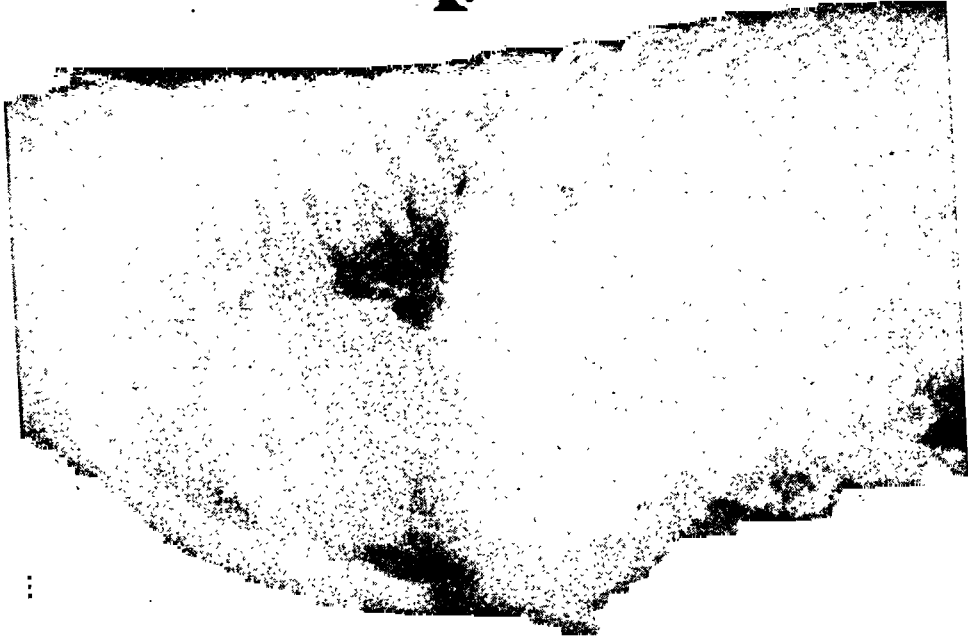
Because no improvement was seen and because corrective surgery in cases of morbus caeruleus has recently been a helpful measure on occasion, the Blalock procedure<sup>15</sup> of anastomosing a sizable branch or tributary of the systemic arterial circulation to the pulmonary artery was thought advisable, the approach in this instance being on the right. The surgical procedure was successful; the right subclavian artery was anastomosed to the pulmonary artery very skilfully.

Postoperatively the child's condition improved, as gauged by a definite decrease in the amount of cyanosis. The respirations, however, continued to be labored and approximately seven and one half hours after the operation the child suddenly took several gasps and died. All supportive forms of therapy in the form of intracardiac adrenalin and coramine were without effect.

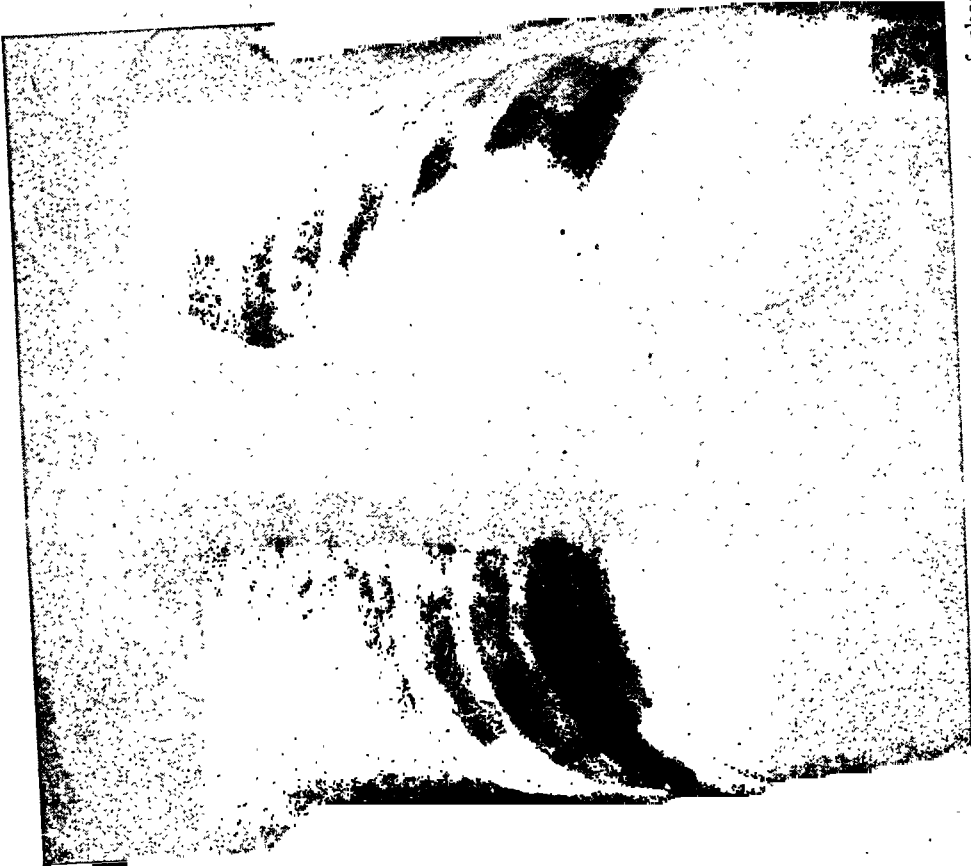
Pathological examination at autopsy showed, on superficial examination, a heart globular in shape and enlarged to the left. It weighed 48.5 grams (the normal for this age is 30 grams). The pulmonary artery and the aorta had proper anatomical relationship. The aortic arch arose normally and passed to the left of the trachea and the esophagus. The innominate artery, left carotid and left subclavian arteries also arose normally. The right auricle was normal in size and showed no appreciable hypertrophy. There was no evidence of a tricuspid valve, the orifice site being closed by a smooth, fibrous structure. The left auricle appeared as a cavity formed by the cavernous dilatation of the pulmonary veins, which had fused before approaching the proximity of the heart. The connection between the atria was a defect in the mid-portion of the intra-atrial septum. The mitral valve was seen to consist of one combined valve cusp, together with two small cusps. The left ventricle was dilated. The ventricular wall measured 7 mm. The interventricular septum had a defect

FIG. 1. Diagrams of course of circulation in

- A—Tricuspid atresia
- B—Eisenmenger's complex
  - P.A.—pulmonary artery
  - S.V.C.—superior vena cava
  - P.F.O.—patent foramen ovale
  - R.A.—right auricle
  - I.V.S.D.—interventricular septal defect
  - I.V.C.—inferior vena cava
  - R.V.—right ventricle
  - AO.—aorta
  - P.V.—pulmonary vein
  - L.A.—left auricle
  - L.V.—left ventricle
- C—Transposition of the great vessels (complete), and
- D—Cor biloculare
  - I.A.—innominate artery
  - L.C.C.—left common carotid artery
  - C.A.—common auricle
  - C.V.—common ventricle



Case 1. Lateral View



Case 1. A-P View

FIG. 2. Roentgenogram of chest in case of tricuspid atresia.

rather high up, which measured 8 mm. in diameter. The aortic valve measured 13 mm., the valve itself being made up of three cusps. The right and the left coronary ostia arose beneath the anterior cusps. The pulmonary valve circumference measured approximately .75 cm. A probe could be passed easily from the left ventricular chamber through the patent interventricular septal defect on into either the aorta or the pulmonary artery. Grossly the remainder of the autopsy was non-contributory.

Of some interest is the finding in the lungs. The right lung had a firm, resilient rubbery consistency. On the lateral surface of the lower lobe there was a friable red blood clot. It had a shaggy surface and was attached to the pleura. The rest of the pleural surface of this lung was blood stained. On section the surfaces of all lobes

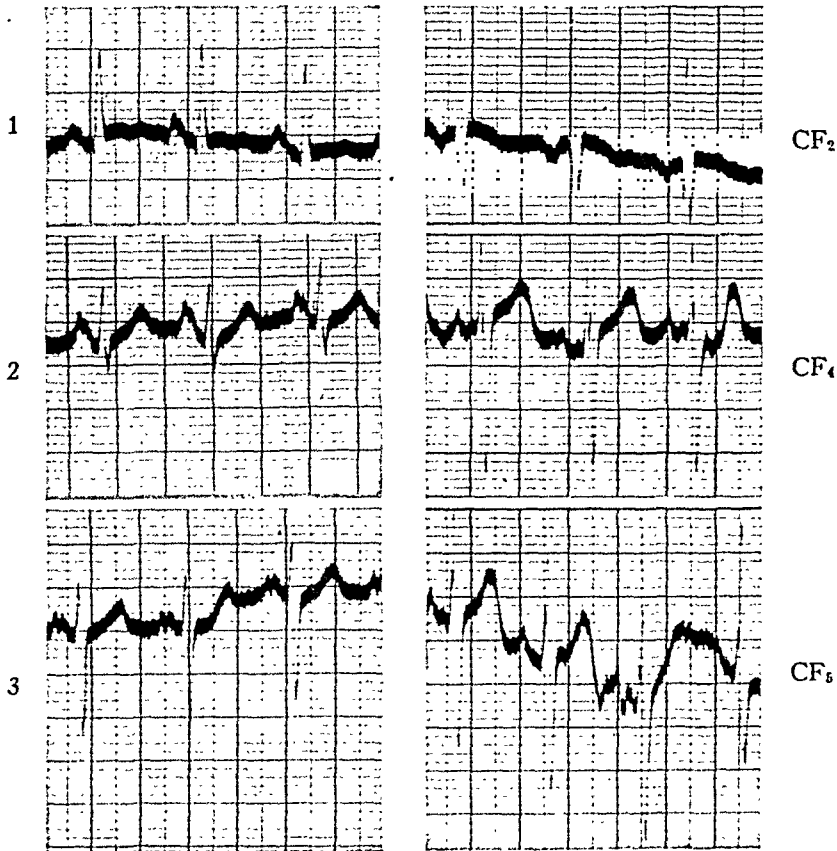


FIG. 3. (Case 3) Electrocardiogram in case of tricuspid atresia. Note: Left axis deviation.

were of a dense pinkish-gray, non-aerated appearance almost like that of ground glass. The color and consistency were uniform throughout. The left lung was crepitant and had a pale gray surface. On section it appeared well aerated throughout.

### DISCUSSION

Among the infrequently seen and less well recognized entities of congenital heart disease embodied in Maude Abbott's classification of persistent cyanosis<sup>1</sup> is included the combination of tricuspid atresia and right ventricular hypoplasia. A brief review of the literature to date reveals that the total number of cases reported amounts to 34 or more. In the past 10 years

there have been only two examples of this complex in the Massachusetts General Hospital files.

Many theories of origin have been advanced, a few of which may be stated. Rauchfuss<sup>18</sup> believed this to be secondary to an overgrowth and fusion of the endocardial cushions which then obliterate the tricuspid orifice. The endocardial cushions are the anlage of the valve leaflets.

Monckeberg<sup>11</sup> believed that the obliteration of the right a-v orifice results from the unequal division of the primitive atrium by an abnormal shifting of the auricular septum chiefly to the right. This was previously advocated by Vierordt.<sup>17</sup>

Abbott<sup>1</sup> suggested that in early fetal life the auricular canal first opens by means of a common orifice into the left side of the common ventricle. Later, by shifting to the right, it comes to lie more in the midline. However, because it does not shift sufficiently to the right, a maladjustment of the part and consequent mitral or tricuspid atresia would occur.

Clinically certain features in combination afford the clue to diagnosis:

(1) Cyanosis, usually noted at birth. This is secondary to the oxygenation of an insufficient amount of blood (Lundsgaard's L factor), by the admixture of arteriovenous blood (Lundsgaard's C factor) and by peripheral capillary stasis (Lundsgaard's D factor).

(2) Left axis deviation in the electrocardiogram. This seems to be the only type known to present a left axis deviation among the persistently cyanotic group as classified by Abbott.<sup>1</sup> Although Tetralogy of Fallot in dextrocardia gives left axis deviation,  $P_1$  inverted, as compared to the upright  $P_1$  in tricuspid atresia.

(3) Left-sided enlargement on roentgen-ray examination. This has been seen invariably. The cardiac shadow takes on a peculiar outline. In the anteroposterior view, because of the absence of the pulmonary conus, the upper contour of the shadow immediately to the left of the sternum has a concave rather than a convex border. In the left oblique position one notes the small size of the right ventricle indicated by the absence of the cardiac shadow anterior to that of the aorta.

(4) Polycythemia, always present, with clubbing in some instances.

(5) Systolic murmur. A loud systolic murmur, best heard in the second and third interspaces just to the left of the sternal line, has been noted at times in a majority of patients. Taussig<sup>2, 23</sup> believes this to be due to the flow of blood in the patent ductus secondary to the relative pulmonic and systemic pressures. Quite likely an interventricular septal defect also plays a part in its production. Many times the ductus is not patent. Peculiarly, when the child is most cyanotic several investigators have noted the disappearance of the murmur. Apparently tricuspid atresia cannot be ruled out by the absence of this murmur.

(6) Other congenital anomalies. Frequently seen in combination are certain compensatory anomalies, namely, patent ductus arteriosus, inter-

ventricular septal defect, patent foramen ovale, and transposition of the great vessels.

In the case reported here the course of blood could be reconstructed with ease (figure 1 A). Entering the heart via the right auricle, the blood was shunted to the left auricle through the patent foramen ovale. From the left auricle it passed to the left ventricle and then out either into the pulmonary artery and the lungs or into the aorta and the systemic system, access to both being afforded by the patent interventricular septal defect. Pathological study would indicate that the obliteration of the tricuspid orifice occurs about the fourth week and the ventricular septum does not close until the eighth. It has been postulated by Bellett<sup>14</sup> that probably the force of blood flowing from the left to the right ventricle prevents the permanent closure of the septum. Many of these patients do not live beyond one year, although a case has been reported by Hedinger<sup>19</sup> in which the duration of life was 56 years. This span was facilitated by a transposition of the great vessels, which favored the circulation.

Vascular surgery in a child of this age is at best quite a difficult technical procedure. We believe that it has been fairly well established by experience up to the present time that if such a procedure is begun but not completed in a patient as severely incapacitated as are the members of this group it will in most instances prove fatal. It may be advisable to withhold attempts towards correction by surgery until the patient has reached a suitable age, presumably around four or five years of age. The gravity of our patient's situation was accentuated by the child's general debility. This, together with the existence of unsuspected congenital anomalies, led to his untoward end.\*

#### *Case 2. Eisenmenger's Complex.*

L. C., a five year old boy, was first admitted to the Children's Clinic at the Massachusetts General Hospital in 1943, three years before the present examination, with the chief complaints of shortness of breath and intermittent cyanosis. By history one could not be sure whether he had been cyanotic at birth, which followed a full term, normal pregnancy. At one year he had much difficulty in retaining his feedings, seemed short of breath, and began to have a definite cyanotic tinge to his lips, particularly after playing. From that time to the present he had been followed closely by the clinic physicians. At the age of three years he presented signs of pulmonary congestion but no other signs of congestive heart failure. During this period some retardation of physical growth was noted, together with an increase in the intensity and constancy of the cyanosis. At five years of age the child was brought to the clinic for the purpose of reevaluation for suitability for the Blalock procedure. The past and family histories were noncontributory. His mother did not have rubella, a rash, or any type of infection during her pregnancy.

On physical examination the child was small for his age. Definite cyanosis of the lips and cheeks, clubbing of the extremities, and mouth-breathing were noted. The tonsils were enlarged but otherwise clear.

\* Since this report was written, Dr. Sylvester McGinn has attended a case of a 10 months old baby girl, who proved at autopsy to have the following defects: tricuspid atresia, right ventricular hypoplasia, patent foramen ovale, an interventricular septal defect, and a pulmonary artery which arose in close proximity to the interventricular septal defect.

The heart was enlarged, with the point of maximal intensity in the fifth intercostal space about 6 cm. to the left of the midsternal line (the midclavicular line measured 5 cm.). Heart sounds were heard with relative ease. There was a Grade 2, pulmonary systolic murmur, which was variable with respiration and position change. The blood pressure was 80 mm. systolic and 55 mm. diastolic.

On examination of the abdomen the liver was barely palpable. No edema of the extremities was noted. Laboratory data were as follows: red blood count 7,000,000 cells per cm., white blood count 8,600 cells per cm., hemoglobin 23 grams, hematocrit 55.8, oxygen content (venous) 18.1 volumes per cent, oxygen capacity 25.8 volumes per cent, oxygen saturation 70.2 volumes per cent.

Roentgen-ray (figure 4) revealed extensive enlargement of the heart shadow in the region of the left ventricle and, to a lesser degree, in the region of the left auricle. There was evidence of enlargement of the right ventricle. The hilar vessels were prominent, and there was accentuation of the lung markings throughout both lung fields. The hilar, as well as the pulmonary, vessels showed a definite pulsation. The aorta was small. These findings were consistent with congenital heart disease.

An electrocardiogram (figure 5) showed normal rhythm at a rate of 115, P-R interval equal to 0.15 second, moderate right axis deviation at an angle of  $136^\circ$ , upright T<sub>1, 2, 3</sub> and inverted T in CF<sub>2, 4, 5</sub>.

During the course of the child's hospitalization the tentative diagnosis of Eisenmenger's complex was made in view of the physical findings, the roentgen-ray film and fluoroscopic evidence of pulmonary congestion, and the right axis deviation by electrocardiogram. He was referred to Dr. Helen Taussig at the Johns Hopkins Hospital, who agreed with this diagnosis. Because of the presence of considerable pulmonary congestion, it was decided that the child was not a fit candidate for the Blalock procedure, which would merely shunt more blood to an already overloaded lung structure. He was digitalized and has been carried along favorably up to the present time.

## DISCUSSION

The embryology of the Eisenmenger complex, consisting of dextro-position of the aorta, interventricular septal defect, right ventricular hypertrophy, and a pulmonary artery which is sometimes normal, sometimes dilated, may be discussed briefly at this point. It is the condition of the pulmonary artery which distinguishes this complex from the Tetralogy of Fallot, accompanied as the latter invariably is by a certain degree of pulmonary stenosis.

Rokitansky<sup>24</sup> believed that the Eisenmenger complex was caused by an abnormality in the rotation of the septum bulbi. Spitzer<sup>22</sup> suggested that the complex represents a type of transposition in which the aorta consists of either an incompletely obliterated left aorta or a reopened right ventricular aorta.

Clinically the following factors seem to be rather constant in this complex: (1) There is a definite, distinct prominence of the pulmonary conus with a "dance" of the hilar shadows by fluoroscopy.

(2) The electrocardiogram generally shows right axis deviation.

(3) The systolic murmur may be variable. Some describe it as best heard in the midsternal region, particularly about the third interspace; others, over the entire precordium.

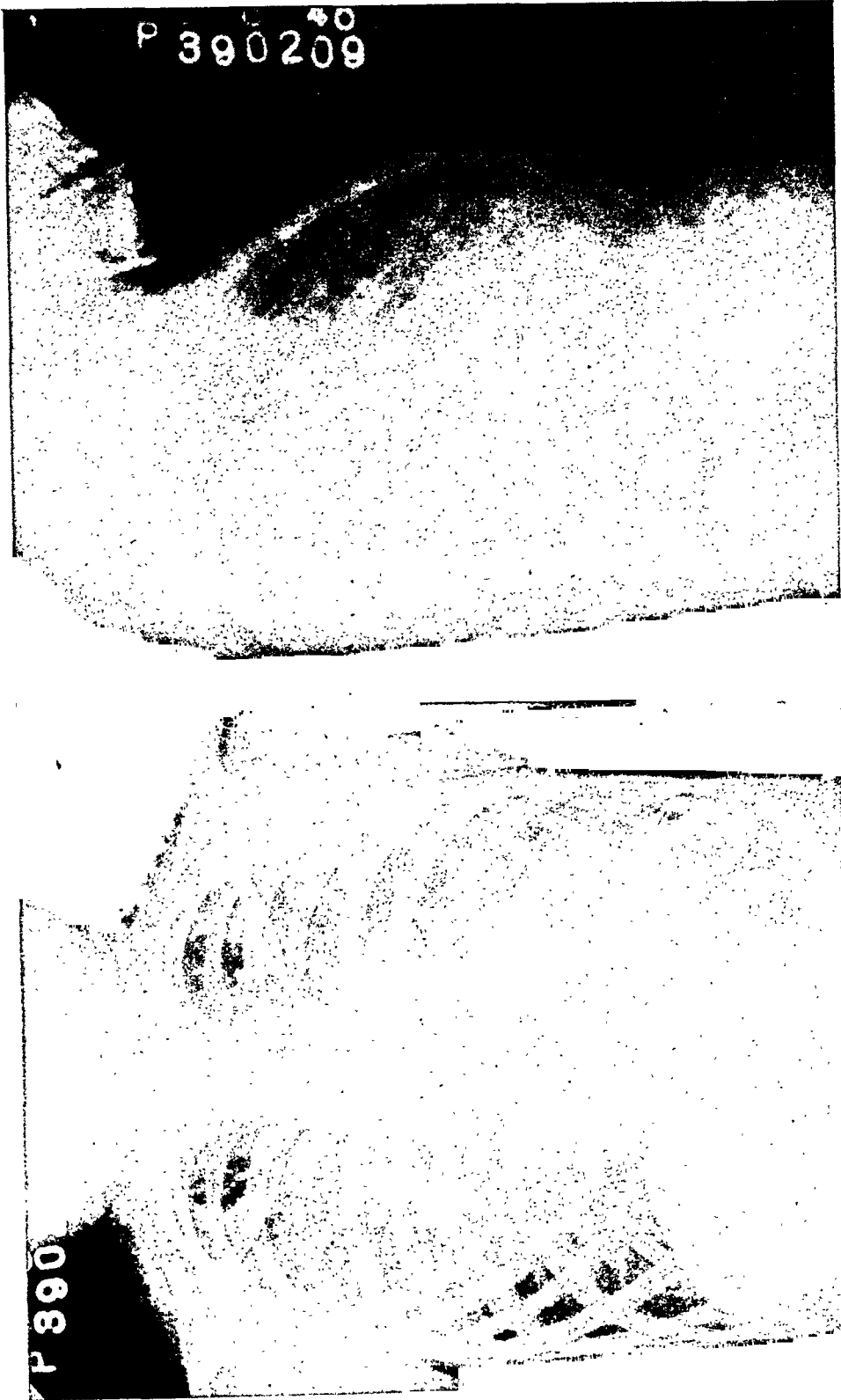


FIG. 4. Roentgenogram of chest in case of Eisenmenger's complex.

Case 2. Lateral View

Case 2. A-P View



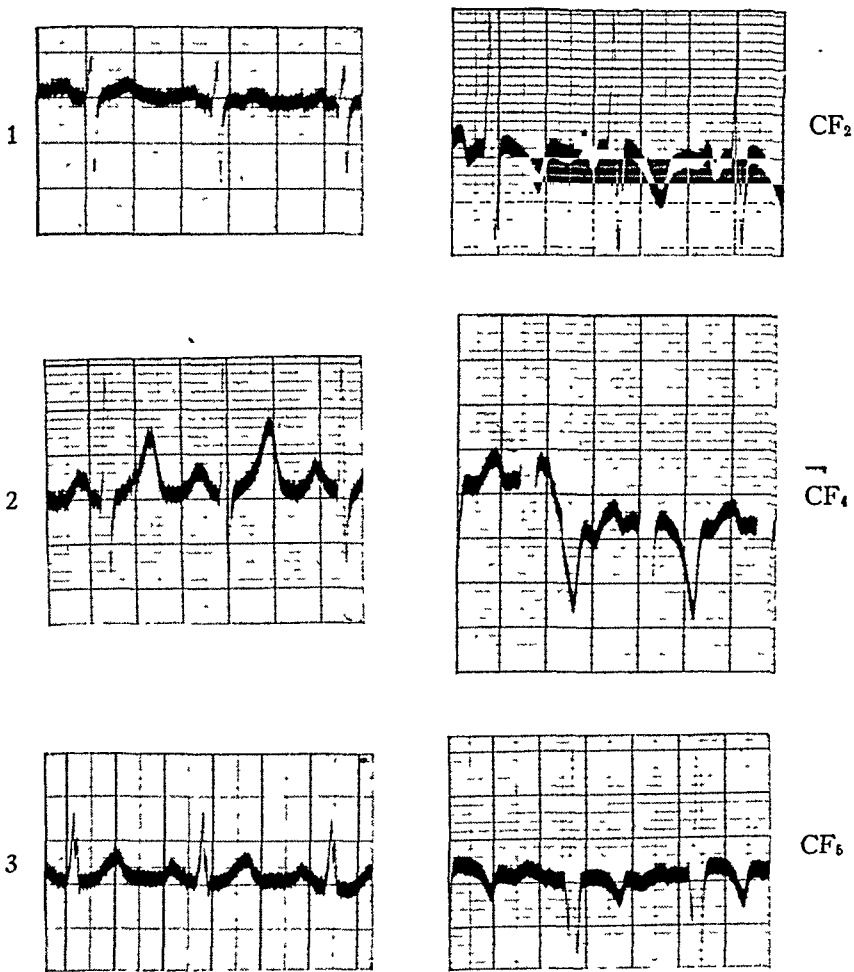


FIG. 5. (Case 2) Electrocardiogram in case of Eisenmenger's complex.  
Note: Right axis deviation.

(4) There seem to be less cyanosis and less clubbing in this complex than in the Tetralogy of Fallot.

(5) At times hoarseness is noted in the Eisenmenger complex because of pressure of the pulmonary conus on the recurrent laryngeal nerve.

(6) Dyspnea may be present, as well as the other, general symptoms of congenital heart disease, such as cough, polycythemia, dysphagia, abnormal susceptibility to infections, weakness, dizziness, convulsions, and tingling of the extremities.

Surgery was avoided in this case, for fear of further burdening of an already overloaded pulmonary circulation. Figure 1 B is a schematic illustration of the heart in the complex of Eisenmenger's complex.

#### *Case 3. Transposition of the Great Vessels.*

H. G., a 17 year old schoolboy, was admitted to the Massachusetts General Hospital on January 15, 1945, with the complaints of dyspnea and cyanosis. Since birth this boy had been noted to be cyanotic, and for as long as he could remember

he had been short of breath on the slightest exertion. Although there had been no progression of his symptoms during recent years, the existing syndrome had remained apparent, with clubbing of the fingers and toes, marked hoarseness, and periods of epistaxis of short duration and mild intensity. For some time he had not brushed his teeth because of ready bleeding of the gums. Because of the tentative diagnosis of Tetralogy of Fallot, the boy was brought into the hospital for the purpose of determining whether or not he would be a fit candidate for the Blalock procedure.

It may be noted here that the tendency to bleed had increased over the years and that his dyspnea had reached a state where it prevented his playing with other children. Mentally he had found it very difficult to keep up with his school work. The family history was non-contributory, and his mother denied any type of rash or infection during her pregnancy.

On physical examination the patient was severely underdeveloped. Otherwise he appeared well except for marked cyanosis of the face and hands and clubbing of the fingers and toes. There were a moderate number of carious teeth in the mouth. The neck showed prominent arterial pulsations, and there was a noticeable prominence of the left anterior chest.

Examination of the heart revealed it regular and moderate in rate and rhythm. The sounds were well heard. The point of maximal intensity was in the fifth intercostal space, 7 cm. to the left of the midsternal line. There were no murmurs audible at either the apex or base.  $P_2$  seemed prominent. No thrills were felt. The blood pressure was 95 mm. systolic and 55 mm. diastolic.

Laboratory data were as follows: urinalyses essentially normal; red blood count 11,800,000; white blood count 4,800; hemoglobin 164 per cent; hematocrit 86; mean corpuscular hemoglobin 16.6 (29); mean corpuscular hemoglobin volume 36 (34); mean corpuscular volume 46 (85); color index 0.56; arterial  $CO_2$  13.4 m.eq. per liter, 29.6 volumes per cent; arterial  $O_2$  content 16.2 volumes per cent; saturation 62 per cent; checked hematocrit centrifuged three hours at 2360 revolutions per minute, 88.2 per cent. A Hinton test was negative.

Roentgen-ray study (figure 6) showed a heart enlarged in the regions of the left auricle and ventricle. The aorta was small. The hilar blood vessels and the blood vessels throughout the structure of both lung fields were prominent, but no pulsations were seen fluoroscopically. Both lungs seemed emphysematous. The diaphragms were low in position but showed good and equal motion. The superior mediastinum was rather wide, probably due to blood vessel structures. These findings were consistent with congenital heart disease and raised the question of transposition of the great vessels.

An electrocardiogram (figure 7) showed sinus arrhythmia at a rate of 110, P-R interval equal to 0.13 second, marked right axis deviation (angle  $+150^\circ$ ) with prominent S-2, upright  $T_{1, 2}$ , with slight depression of the S-T intervals in these leads, upright T in  $CF_{2, 4, 5}$ . Of significance, then, in this electrocardiogram was the right axis deviation.

Throughout this boy's hospitalization the diagnosis of Tetralogy of Fallot or some extreme variation thereof was thought most likely by all members of the surgical and cardiovascular departments. Therefore it seemed feasible to offer the patient the expedient of surgery. Before operation the hematocrit level was reduced to 55-60 by repeated small venesections, replacing the blood volume by plasma. Digitalization was carried out because of the cardiac enlargement. On February 2, 1946, the Blalock procedure was attempted, in this case anastomosing the right subclavian artery to the right pulmonary artery, but the operation could not be completed because of the anatomical vascular anomalies unexpectedly encountered. The chest was closed without any definite surgery having been accomplished. Approximately seven and one half hours after operation the patient died.

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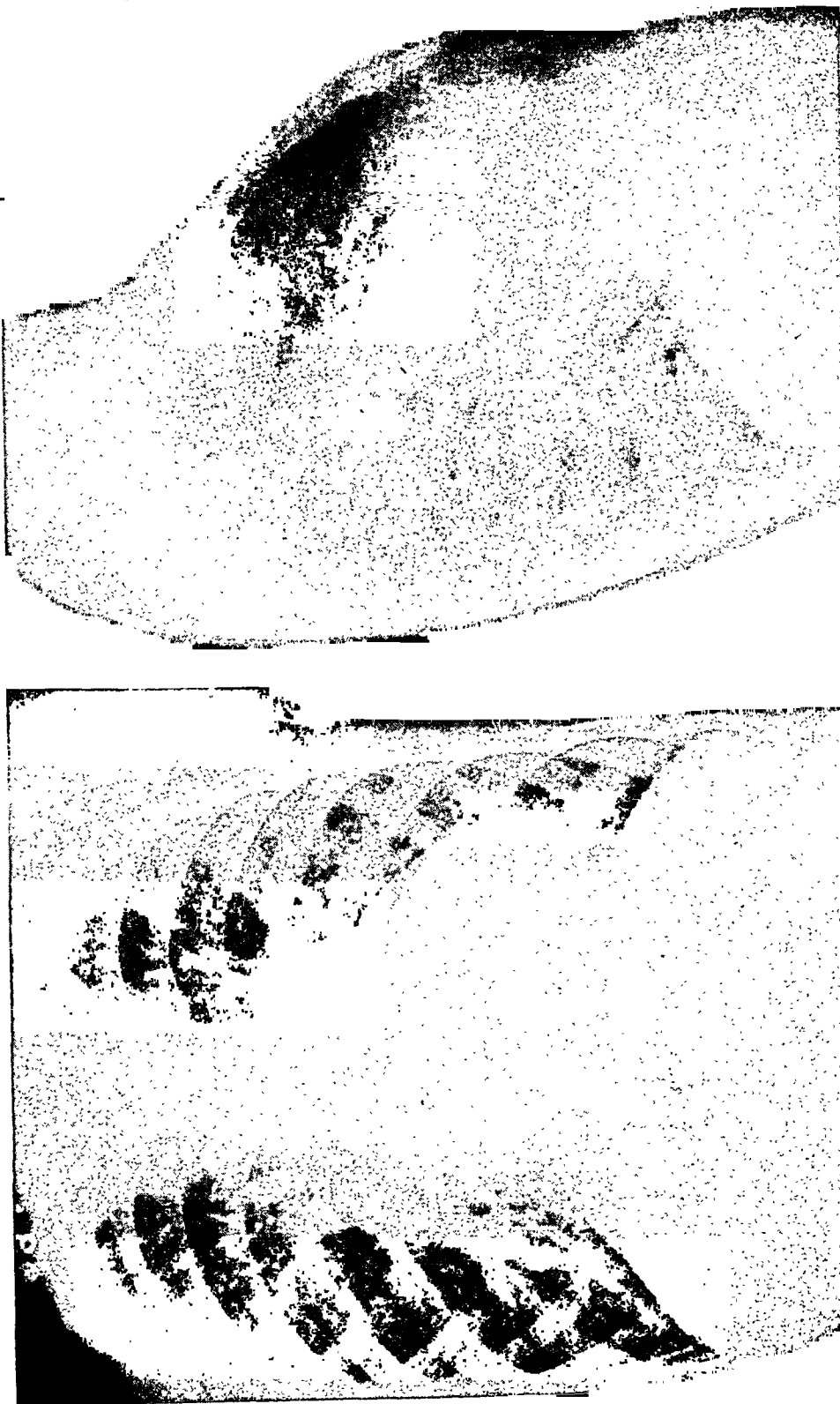


FIG. 6. Roentgenogram of chest in case of transposition of the great vessels (complete).

Case 3. A-P View

Case 3. Lateral View

Postmortem examination revealed the body of a 17 year old boy measuring 135 cm. and weighing approximately 60 pounds but having the appearance of a child of about 10 years of age. There was 4+ clubbing of the fingers and toes. The heart weighed approximately 250 grams. There was a transposition of the origins of aorta and pulmonary artery. The right and left ventricular walls measured 7 mm. Other measurements were as follows: tricuspid ring to the apex 6 cm., mitral valve 7.5 cm., aortic valve 6 cm., tricuspid valve 9.5 cm., and pulmonary valve 6 cm. There were numerous plaques in the pulmonary artery, some calcified. The pulmonary valve was bicuspid. Friable adhesions were present on one of the cusps of this valve. The

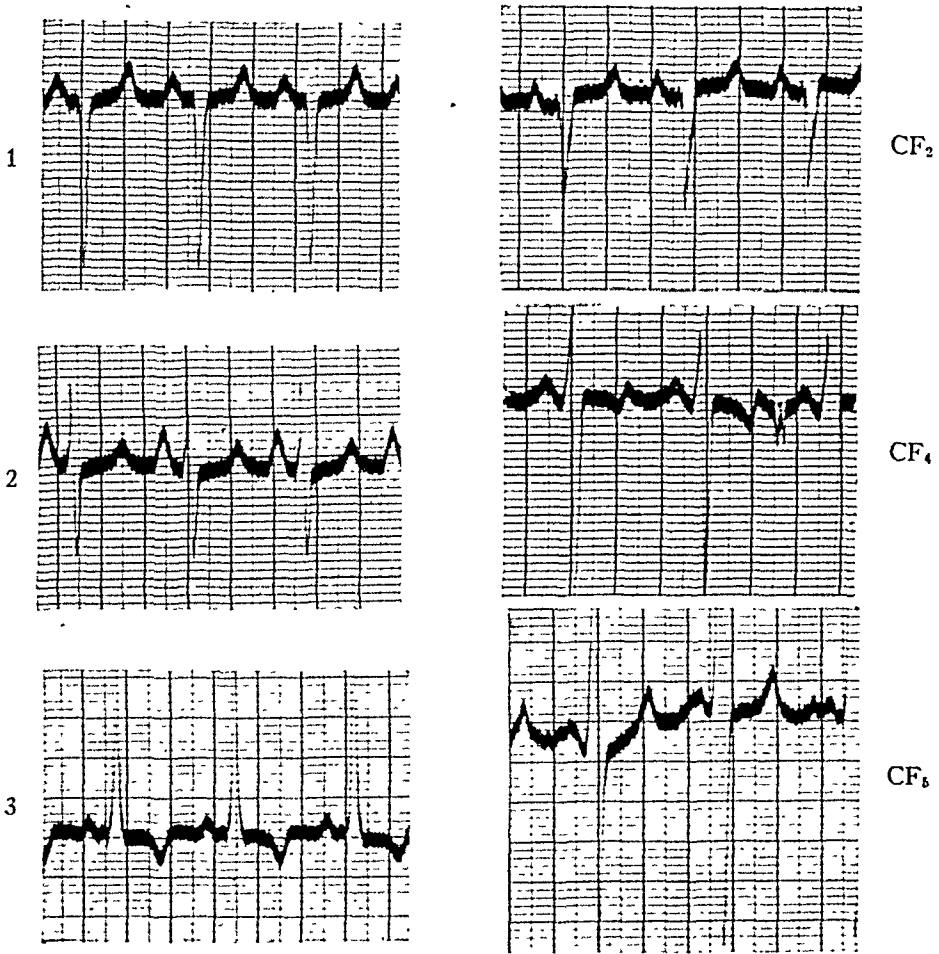


FIG. 7. (Case 3) Electrocardiogram in case of transposition of the great vessels (complete).  
Note: Right axis deviation, prominent S in Leads  $CF_4$  and  $CF_6$ .

cavities of the right and the left ventricles appeared to be of about the same size. There was a patent foramen ovale. The coronaries were also patent. Figure 1 C is a schematic representation of the heart in this case of complete transposition of the great vessels.

The trachea and bronchi were filled with clear yellow fluid. The lungs weighed approximately 655 grams. Over the left lower lobe the pleura was ragged because of adhesions. Cut sections revealed edematous lungs which were mildly congested. The right pleural cavity contained about 50 c.c. of dark red blood. The diaphragmatic and visceral pleura were adherent over the left diaphragm. Liver weight was 820 grams; on section this organ appeared to be darker than is usual.

## DISCUSSION

Transposition of the great vessels offers a problem in embryology for which many ideas have been postulated. Fundamentally most writers account for the unusual position of the vessels by detorsion of the heart tube in this region and an unwinding of the dextral spiral. Spitzer<sup>22</sup> suggests that the incomplete torsion leads to a fusion of the primary bulbar septum and a reopening of the right reptilian aorta with obliteration of the left. Seemingly, then, the aorta in transposition is not a transposed aorta but a reopened right aorta. What part abnormal absorption of the bulb plays in this process is controversial.

Bremer<sup>20</sup> theorizes that continued growth of the bulb in a dorsal position meets with opposition by the diaphragm, thus forcing the right ventricle to be displaced ventrally. Because of the attachment of the right ventricle to the intraventricular canal, it is suggested that there is a rotary, counterclockwise motion which counteracts the normal dextrotorsion when transmitted to the bulb and that this in turn gives rise to transposition.

Transposition of the great vessels may at least be suspected when a goodly number of the findings listed herewith are present: growth difficulties, cyanosis and dyspnea, spells of fainting, increased red blood count, a variable murmur (apical systolic at times); also when roentgen-ray findings show enlargement of both ventricles, the contour of the right being due to the enlargement of the right ventricle, that on the left being due to enlargement of the right ventricle or both ventricles; when the electrocardiogram shows right axis deviation; and when some minor signs are present, such as enlargement of the liver and spleen, edema of the extremities, or choking cough.

Surgery as it exists today would obviously be of no benefit in this type of case and should be avoided after the correct diagnosis is made.

*Case 4. Cor Biloculare.*

J. W., a one month old baby boy, was admitted to the Massachusetts General Hospital on March 21, 1946, with the complaint of intermittent attacks of cyanosis over a period of one week. The infant had been delivered by forceps at full term, his birth weight being 5 pounds, 4 ounces. Even though he was not a blue baby at birth, the neonatal course was rather stormy. An oxygen tent was employed for some days because of his difficulty in breathing. While in the hospital he received massage treatment for a deformed left arm. At home he took his formula well and seemed quite content.

About one to two weeks later it was noted that the child turned blue after one of his crying spells. Because these blue spells recurred three to four times each week and the duration increased from three to 30 minutes, the infant was brought to the hospital by his parents. The mother stated that the baby seemed to lose consciousness during the spells. Family history was noncontributory. The mother denied having had a rash or German measles or any type of infection during her first three months of pregnancy. There were no siblings.

On physical examination the child was fairly well developed, although he appeared both dyspneic and cyanotic. His temperature was 99, his pulse 160, and his

respirations were 70. He seemed very restless. The chest was clear to percussion and auscultation except for a few musical râles at the base.

Heart size was slightly increased on physical examination. The rhythm was regular, the rate rapid. Heart tone and quality were fair. There was a Grade 3, systolic murmur at the apex.

Examination of the abdomen revealed the liver edge palpable 3 cm. below the costal margin. The left forearm was slightly deformed, with only four fingers on the left hand. There was a moderate scoliosis.

Complete blood count showed 5,400,000 red blood cells per cu. mm., 7,100 white blood cells per cu. mm., polymorpholymphocytes 70 per cent, lymphocytes 30 per cent. A roentgen-ray film was unobtainable because of the child's grave condition.

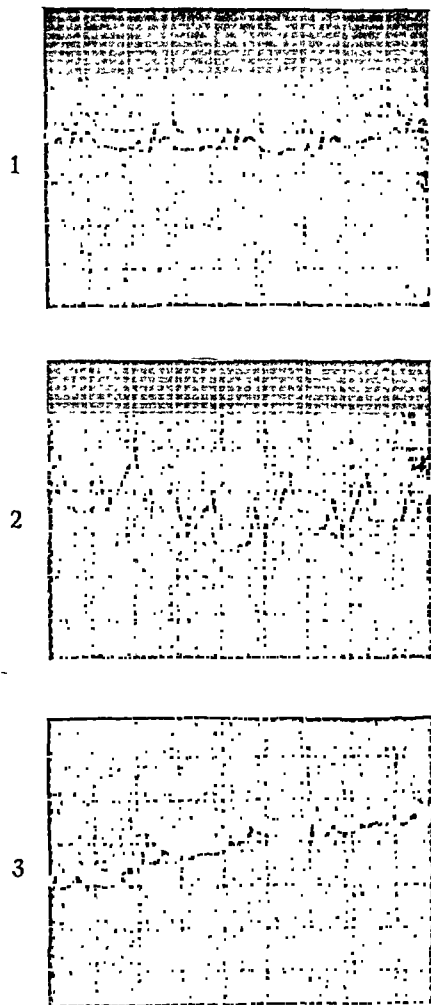


FIG. 8. (Case 4) Electrocardiogram in case of cor biloculare. Note: Right axis deviation.

An electrocardiogram (figure 8) showed a sinus tachycardia at a rate of 154, P-R interval equal to 0.08 second, right axis deviation (angle =  $+172^\circ$ ) with prominent  $S_2$ , upright  $T_{1,2}$  and low upright  $T_3$ . The right axis deviation is the finding of significance.

On entry into the hospital the patient was placed in an oxygen tent. Temporarily he seemed much better, his heart sounds improved in quality, and the cyanosis lessened. During the first two days he was digitalized with 0.1 mg. of lanatoside-C (Cedilanid)

intramuscularly, followed by a maintenance dose of 15 mg. of the digitalis leaf. Skimmed milk feedings were accepted. His condition improved during the next two days to such an extent that he was allowed out of the tent for variable periods. Four days after admission the resident was called to see the infant because of a sudden episode of rather intense cyanosis with poor response on stimulation. The pulse was 72; respirations were 120. The baby seemed sluggish, and there was evidence of poor peripheral circulation. Because of his severe dyspnea, oxygen was administered to the child by mask, following which he improved for a while. The râles at the base persisted, as did his murmur, and although his color improved the child remained very ill.

Two and one half hours after this episode he again became deeply cyanotic despite the oxygen and the continued use of stimulants and suddenly cease to breathe. Artificial respiration and the intracardiac use of adrenalin were of no avail. The discharge diagnosis was congenital heart disease, probably a septal defect with resultant respiratory and cardiac failure.

On autopsy the body was that of a malnourished white male infant, measuring approximately 50 cm. in length and weighing 2,500 grams.

The heart was found to lie in a transverse position in the thorax with two vessels 13 mm. in diameter arising from a common ventricular chamber. The anterior vessel divided into branches to supply the pulmonary artery and then continued in the course of the aorta upward, backward, and downward. The posterior vessel passed upward behind the first vessel and branched in the superior mediastinum into the innominate, the left internal carotid, and the left subclavian arteries. It then sent a 6 mm. communicating branch to the other vessels and terminated in the left subclavian artery. There was a single common auricular chamber receiving the venae cavae on the right as well as the right pulmonary veins. The left pulmonary veins emptied into the left side of this chamber. A single four-cusped auriculoventricular valve separated the auricle from the ventricle. The myocardium was firm and averaged 8 to 11 mm. in thickness. The cor biloculare which was thus encountered is schematically shown in figure 1 D.

The lungs were pink and well aerated anteriorly. They were subcrepitant posteriorly and in their dependent portions. Grayish-pink to pinkish-red colorations were seen on section, dark red blood oozing from the cut sections. The liver weighed 86 grams. Its edge measured 3 cm. below the costal margin. On examination the capsule was tense and on section dark red blood was seen to ooze from the cut areas. There were multiple deformities of the skeleton with an absence of the radius and the thumb on the left upper extremity and a marked scoliosis of the spine due to hemivertebrae in the region of T-9 to T-11.

## DISCUSSION

Complete cor biloculare is a rare finding, either with division of the truncus arteriosus as here described or without division. One would assume with such an anomaly that there has been arrest in development before the fourth week, that is, before the appearance of the cardiac septa. Clinical recognition of this congenital abnormality as a single entity would appear to be impossible, although there are a few findings which bear mention in this respect. First, there is usually found some degree of cyanosis. Its time of onset is as variable as its intensity, but if the patient lives for a few months at least its presence is always noted. As variable as the cyanosis is the presence of murmurs. Generally there is a systolic murmur heard over

the entire precordium. Usually there is a rather definite degree of right axis deviation by electrocardiogram and an enlarged globular heart by roentgen-ray. Clubbing may or may not be as evident as the other findings consistent with the diagnosis of congenital heart disease.

Obviously surgery would be more detrimental than helpful in a case such as this and in similar cases of more advanced years. As mentioned above, a definite dogmatic diagnosis of such a condition is quite impossible. It may be stated that recently two procedures of diagnostic value, namely angiography and cardiac catheterization with blood gas determinations, have been used to great advantage. The value of the inclusion of these measures in the armamentarium of the diagnostic clinic cannot be overemphasized.

### SUMMARY

1. Cases have been presented to illustrate four noteworthy congenital cardiac conditions causing cyanosis which must be differentiated from the more common Tetralogy of Fallot. These four conditions are Tricuspid Atresia, Eisenmenger's Complex, Transposition of the Great Vessels, and A Single Ventricle.

2. Emphasis has been placed in this paper on the case of Tricuspid Atresia and also on its clinical features, which render it a definitely diagnosable entity. The case herewith presented is that of a five and one-half month old boy in whom periodic attacks of cyanosis were noted by the mother and who showed on physical examination a generalized slate-blue color, a Grade 4 systolic murmur in the second and third interspaces just to the left of the midsternal line, and also a palpable liver. By electrocardiogram he presented definite left axis deviation, by roentgen-ray an enlarged heart with no evidence of pulmonary engorgement.

3. A case of probable Eisenmenger's Complex has been described and discussed briefly. This was a five year old boy who complained of intermittent attacks of shortness of breath and cyanosis and on physical examination demonstrated a rather persistent cyanosis, an enlarged heart with a Grade 2, systolic murmur, and a barely palpable liver. Roentgen-ray of the chest showed pulmonary congestion. The electrocardiogram showed right axis deviation.

4. Description of a case of Transposition of the Great Vessels with explanatory notes referable to its embryology and clinical findings was presented. The patient was a 17 year old boy who was said to have been short of breath and cyanotic for the greater part of his life and to have been hoarse and to have manifested some degree of epistaxis only within recent months. Physical examination revealed chiefly a deep cyanosis, clubbing of the digits and toes, an enlarged heart, without murmurs or evidences of pulmonary congestion. Roentgen-ray confirmed the heart size and suggested the possibility of transposition of the great vessels. An electrocardiogram demonstrated right axis deviation.



5. Lastly, a case of A Single Ventricle was described. The child, a one month old boy, was noted to have periodic episodes of cyanosis and also some difficulty in breathing. By physical examination he was moderately dyspneic and cyanotic with an enlarged heart, a Grade 3 systolic murmur at the apex, and a palpable liver. Right axis deviation was prominent in the electrocardiogram.

## BIBLIOGRAPHY

1. ABBOTT, MAUDE E.: Atlas of congenital heart disease, 1936, Am. Heart Assoc., New York.
2. TAUSSIG, HELEN: The clinical and pathological findings in congenital malformations of the heart due to defective development of the right ventricle associated with tricuspid atresia or hypoplasia, *Bull. Johns Hopkins Hosp.*, 1936, lix, 433.
3. GIBSON, S., and CLIFTON, W. M.: Congenital heart disease: a clinical and post mortem study of 105 cases, *Am. Jr. Dis. Child.*, 1938, lv, 761.
4. HARRIS, J. S., and FARBER, S.: Transposition of the great cardiac vessels with special reference to the phylogenic theory of Spitzer, *Arch. Path.*, 1939, xxviii, 427.
5. WALLS, E. W.: Biatrinal trilocular heart with atresia of the mitral valve, *Lancet*, 1941, ii, 668.
6. KRUMBHAAR, E. B.: A congenital cardiac anomaly, *Jr. Mt. Sinai Hosp.*, 1942, viii, 737.
7. SAKAKI, J.: Ein Sektionsfall von seltner Herzmissbildung sogenanntes Cor Trilocular Biatrium univentriculare mit der sogenannten kirkirngerten Transposition der grossen Gefässe und der sogenannten Tricuspidalatresie, *Mitt. d. med. Gesellsch. zu Tokyo*, 1938, lii, 1037.
8. MANHOFF, L. J., and HOWE, J. S.: Congenital heart disease: tricuspid atresia and mitral atresia associated with transposition of the great vessels, *Am. Heart Jr.*, 1945, xxix, 90.
9. KUHN, M.: Über zwei Fälle kongenitaler Atresia des Ostium venosum dextrum, *Jahrb. f. Kinderh.*, 1906, lxiii, 235.
10. BERNSTEIN, E. P.: Case of congenital heart disease, *Proc. N. Y. Path. Soc.*, pp. 29, 1906.
11. MONCKEBERG, J. G.: Die Missbildungen des Herzens in HENKE, F. and LUBARSH, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, 1924, ii, 1, J. Springer, Berlin.
12. WIELAND, E.: Zur Klinik und Morphologie der angeborenen Tricuspidalatresie, *Jahrb. f. Kinderh.*, 1914, lxxix, 320.
13. RIHL, TERPLAN, WEISS: Über einen Fall von Agenesie der Tricuspidalklappe, *Med. Klin.*, 1929, xxv, 1543.
14. BELLETT, S., and STEWART, H.: Atresia of the tricuspid orifice, *Am. Jr. Dis. Child.*, 1927, xlv, 6.
14. BELLETT, S., and STEWART, H.: Atresia of the tricuspid orifice, *Am. Jr. Dis. Child.*, 1927, xlv, 6.
15. BLALOCK, A., and TAUSSIG, H.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 189.
16. BROWN, J. W.: Congenital tricuspid atresia, *Arch. Dis. Child.*, 1936, xi, 275.
17. VIERORDT, H.: Primäre Fehler am Ostium venosum dextrum, in NOTHNAGEL, C. W. H.: *Spezielle Pathologie und Therapie*, Vienna, 1901, xv, 2.
18. RAUCHFUSS, C.: Die angeborenen Entwicklungsfehler und die Fötalkrankheiten des Herzens und der grossen Gefässen in GERHARDT's *Handbuch der Kinderkrankheiten*, 1878, iv, 99, H. Laupp, Tübingen.
19. HEDINGER, E.: Transposition der grossen Gefässe bei rudimentären linker Herzkammer bei in 56 jährigen Frau, *Centralbl. f. allg. Path. u. path. Anat.*, 1915, xxvi, 529.

20. BREMER, J. L.: Transposition of the great vessels, *Arch. Path.*, 1942, xxxiv, 1016.
21. SAPIR and LEV: Tetralogy of Eisenmenger, *Am. Heart Jr.*, 1945, ii, 3.
22. SPITZER, A.: Über den Bauplan des normalen und missbildeten Herzens, *Virchow's Arch. f. path. Anat.*, 1923, ccxliii, 81.
23. TAUSSIG, H.: Clinical and pathological findings in congenital malformation of the heart due to defective development of right ventricle associated with tricuspid atresia or hypoplasia, *Bull. Johns Hopkins Hosp.*, 1936, lix, 435.
24. VON ROKITANSKY: Die Defecte der Scheidewände des Herzens. *Pathologishanatomische Abhandlung VI (21)*: 156, pp. 11, fol. Wien, W. Braumüller, 1875.

# NEPHROGENIC DIABETES INSIPIDUS: TRANSMITTED BY FEMALES AND APPEARING DURING INFANCY IN MALES\*

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THIS paper reports an unusual type of diabetes insipidus. This entity has most likely existed before, but we have not found any evidence of its recognition as such. Before discussing the characteristics of the syndrome, a presentation of our studies is given, chiefly in the order that they were conducted.

*Patient C. H.* A physician, aged 35, was recently admitted to the Boston City Hospital with pneumonia. His past health had been good, but he stated that he had had diabetes insipidus since infancy. In the course of treating the pneumonia with sulfadiazine it was observed that the concentration of this compound in the blood was unusually high in spite of a daily urine volume of about 12 liters. This observation and the fact that several members of the family had had diabetes insipidus since childhood aroused special interest.

This patient, like six others in five generations of his family, was told that he was a "water baby." When he was one month of age, or younger, his parents noticed that he desired excessive amounts of fluid and that he had a large urine volume. In spite of the persistence of these symptoms, his growth and development proceeded fairly well. However, he never appeared to be very strong and he did not grow to be as large as the average individual, although he had good stamina. His appetite has not been very remarkable, but he never has had much desire for sweets or salt. He has had a great desire for fruit and he has used black pepper freely. He likes meat moderately well.

He has known for eight years that he had hypertension, the systolic blood pressure ranging from 130 to 140 mm. of mercury and the diastolic pressure from 90 to 95. During this time his urine has been examined many times, but it has never been found to contain albumin, sugar or formed elements. The daily urine volume has been determined occasionally and it has been found to vary from 8 to 24 liters per day, with a specific gravity of about 1.001. The ingestion of sodium chloride caused a moderate increase in thirst. On two occasions water was denied for about seven hours and the patient developed a circulatory collapse each time. In 1940 he was given, intramuscularly, 1 c.c. of pitressin tannate in oil every two days for eight days, but this treatment caused no decrease in the urine volume. Large doses of sodium bicarbonate caused a slight decrease in the amount of urine excreted.

He occasionally has had headaches, but these do not tend to be severe. There have been no visual complaints, sensitivity to cold, brittleness of hair or nails, drowsiness nor gonadal disturbances. A careful systemic review elicited no additional complaints.

On physical examination the patient was found to be smaller than average. His weight was 120 pounds and his height was 5 feet and 6 inches. He appeared

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somewhat older than his age of 35 years. The skin was quite unusual in texture and appearance, being pale, shiny, scaly, very dry, coarse, inelastic and parchment-like. The epidermal layer was distinctly thickened. Systolic blood pressure varied from 130 to 175 and the diastolic pressure ranged from 80 to 125. The fundi, thyroid, heart, lungs, abdomen, sexual hair, gonads and neurological examination appeared to be normal.

The urine was pale and the specific gravity was 1.001–1.002. It contained no albumin, sugar, or formed elements. The hemoglobin varied from 82 to 95 per cent of normal. The red blood cell count was 4,300,000 and the volume of packed red blood cells was 42 per cent. Four estimations of the non-protein nitrogen of the blood yielded normal values. The carbon dioxide combining power of the plasma was 42 volume per cent on two occasions. Estimations of creatinine yielded 1.1 and 1.2 mg. per 100 c.c. of blood. The concentration in the serum of sodium, potassium and chloride was normal or slightly elevated (table 1).

TABLE I  
Electrolytes in Serum

Date	Sodium, m.eq./l.*	Potassium, m.eq./l.*	Chloride, m.eq./l.*
6/20	139.9	4.3	113
6/20	140.0	4.2	108.5
11/24	136.5	4.6	102.2
11/26	142.2		110.5
11/28	146.0	5.0	115.0

\* All of the specimens were taken while the patient was in a fasting state, but the amount of water previously ingested varied.

The basal metabolic rate was plus 26 per cent of normal. With the patient in a fasting state there were 120 mg. of glucose per 100 c.c. of blood. After the administration of 75 gm. of glucose, orally, the blood glucose concentration after 30, 60, and 120 minutes was 170, 210, and 180 mg. per 100 c.c., respectively. Another test was conducted, administering 75 gm. of glucose, orally, and 0.1 unit of insulin per kilogram of body weight, intravenously. There were 100 mg. of glucose per 100 c.c. of blood before this treatment was given and after 60, 120, and 220 minutes were 140, 120, and 100 mg., respectively. No sugar appeared in the urine. These tests can be interpreted as indicating the existence of diabetes mellitus with possibly slight insulin resistance. There were 8.9 mg. of 17-ketosteroids excreted in the urine per 24 hours. Roentgenograms of the skull, lumbar vertebrae, pelvis, chest, and abdomen revealed no abnormalities.

The average daily excretion of urine during an interval of 17 days was 10,600 c.c. Several compounds were administered, consecutively, in an effort to modify the volume of urine. The quantity of the latter was determined at frequent intervals throughout the day in order to detect any brief effect that might be exerted. Twenty mg. of desoxycorticosterone acetate in oil when injected, intramuscularly, had no effect. Ten c.c. of adrenal cortical extract was without effect. Potassium chloride, given in doses of 2 gm. six times daily, caused a slight decrease in thirst and in the urine volume.

When 1 c.c. of pitressin tannate in oil was given, intramuscularly, no definite decrease in urine volume resulted, but within 30 minutes after the

injection the patient had a slight chill and a rise in his temperature to 101° F. A few days subsequently he was given 0.1 c.c. of pitressin, intradermally, in the forearm. Within 30 minutes a violent local reaction had developed. At the site of injection there was a firm, white wheal, about 10 by 6 cm. Extending towards the shoulder was an edematous streak which was about 15 cm. long. The reaction was soon inhibited by the injection of 15 c.c. of saline containing  $\frac{1}{2}$  c.c. of 1:1,000 dilution of adrenalin.

The marked allergic reaction to pitressin was considered as possibly accounting for the absence of its antidiuretic effect. In order to test the antidiuretic effect of large doses of pitressin, the patient was desensitized to this solution. Beginning with 0.1 unit of pitressin and progressively increasing the dosage, 17 injections of this drug were given within 30 hours. At the end of this time no local or general allergic reaction to pitressin resulted, even in doses of 1 c.c. (20 pressor units), but there was only a very slight, if any, antidiuretic effect. The phenomenon was regarded as possibly analogous to that observed in three patients with diabetes mellitus, seen by one of us (R. H. W.), who had local inflammatory reactions to insulin and showed no response in the blood sugar to injections of more than 100 units of insulin.

The question for consideration was whether antibodies had been produced which were capable of destroying the pitressin. Studies were conducted with rats to test this hypothesis.

To 0.9 c.c. of the patient's serum was added 0.1 c.c. of pitressin and the mixture, after sitting at room temperature for one hour, was injected, intravenously, into rats. The antidiuretic effect of this solution was tested by the method of Ham and Landis.<sup>1</sup> The control solutions for the experiment consisted of: (a) 0.9 c.c. of serum from a normal man plus 0.1 c.c. of pitressin (2 pressor units), (b) 1 c.c. of normal serum, (c) 1 c.c. of patient's serum, (d) 0.9 c.c. of saline and 0.1 c.c. of pitressin, and (e) 1 c.c. of saline. Each of these solutions was given intravenously to a group of three male rats, each weighing approximately 300 gm. The animals given sera with pitressin added excreted 25 per cent less urine than those given any of the other solutions. Therefore, it was concluded that under the conditions of the experiment the serum did not inactivate the pitressin.

The next question was whether pitressin was inactivated in the patient's body at an abnormally rapid rate. To test this possibility 1 c.c. of pitressin was administered subcutaneously to the patient and a similar injection was given to a normal individual. Thirty minutes later blood was withdrawn and a few minutes thereafter 2 c.c. of serum was injected intraperitoneally into rats. The urine flow was then followed for the next three hours. The serum from the untreated normal subject had no antidiuretic effect whereas the sera of the subjects injected with pitressin had a marked antidiuretic effect.

After giving the patient as much as 3 c.c. of pitressin (60 pressor units)

within six hours, no more than a very slight antidiuretic effect was observed. The above experiments with the rats had indicated that inactivation did not seem to take place abnormally rapidly. Furthermore, after the injection of 0.5 c.c. or more of pitressin, there was generalized blanching of the skin and abdominal cramps, as well as an increase in the blood pressure. Therefore, it was evident that the pitressin was exerting several of its systemic effects, but was failing to affect the reabsorption of water by the kidneys.

These observations suggested that there might be an anatomical, or at least a physiological, defect in a specific segment of the renal tubules. At this point the possibility that there was an even greater production of posterior pituitary principle was considered, since it was believed that the patient often was in a state of dehydration, which Gilman and Goodman<sup>2</sup> found usually leads to an increased availability of the antidiuretic hormone. Moreover, the patient's pallor and hypertension might possibly have been related to increased function of the posterior pituitary lobe. His serum was given to rats, intravenously, in doses of 1 c.c. and its antidiuretic effect was tested in the manner described above. Control specimens of serum were taken from two normal individuals. Another sample of serum was obtained from a normal subject who had drunk 7,000 c.c. of water during the 24 hours previously. Saline was injected into other animals to serve as additional controls. However, no antidiuretic effect was found to be exerted by the serum of any of the subjects.

A series of tests was conducted to establish the extent and site of impairment of renal function. The patient and a normal individual who was essentially the same size were compared in their capacity to excrete sodium chloride. The control subject had a normal blood pressure and phenol-sulphonphthalein excretion; routine examination of the urine revealed no abnormalities. Each individual was in a fasting state and had had no water for one hour. The subjects were asked to void and this specimen was discarded, but hourly collections of urine were made during the next four hours. No treatment was given during the first hour, but throughout the next 45 minutes an intravenous infusion of 1,500 c.c. of normal saline was given at a fairly constant rate. Specimens of blood were taken at hourly intervals. Estimations were made of the sodium and chloride in the blood and urine (table 2). During the one hour control interval each subject excreted about the same amount of sodium and chloride, although the patient excreted more than twice as much urine as did the normal subject. During the hour following the beginning of the saline infusion the patient excreted distinctly less of these electrolytes than did the normal individual, but during each of the subsequent two hours the reverse was found. Throughout the entire four hours the patient excreted about 32 per cent more sodium and chloride than did the normal individual, yet the urine volume was about 300 per cent greater. The chloride concentration of the serum increased markedly in the patient, but it did not show any significant change in the normal subject.

TABLE II  
Rate of Excretion of Sodium and Chloride  
(After the infusion intravenously of 1,500 c.c. of normal saline)

Subject	Hourly Intervals	Urine					Serum	
		Volume, c.c.	Sodium		Chloride		Sodium, m.eq./l.	Chloride, m.eq./l.
			m.eq./l.	total m.eq.	m.eq./l.	total m.eq.		
Normal	Control	150	20.4	3.1	41.8	6.3	140	110
	1	135	96.2	13.0	111.2	15.1	138.5	108.9
	2	145	66.4	9.7	85.0	12.3	141	107
	3	142	101.9	14.5	132.1	18.7	—	—
Patient C. H.	Control	380	6.9	2.62	16.7	6.3	142	106.2
	1	480	12.1	5.8	23	11.0	140	118.5
	2	810	25.8	20.9	30.3	24.5	143	122
	3	680	35	23.8	40.3	27.4	140.8	117.5

During the course of this test the individual with diabetes insipidus became pale, weak and intensely thirsty. He also had a slight drop in his blood pressure.

Following the injection, intravenously, of 1 c.c. of phenolsulphonphthalein, there was found: none in the urine within 15 minutes, 5 per cent after 30 minutes, 15 per cent after 60 minutes, and 20 per cent after 120 minutes. There was also impairment in the clearance of the blood of urea and of creatinine from the plasma (table 3). Despite the marked diuresis, sodium and potassium were eliminated from the body less rapidly than normal, probably indicating increased tubular reabsorption of these elements. In three patients with diabetes insipidus of the "pituitary type," studied by

TABLE III  
Renal Clearance of Blood and Plasma

Subject	Urine, c.c./min.	Clearance, c.c./min.				
		Blood	Plasma			
			Urea	Creatinine	Sodium	Potassium
Normal	1	75	175	3.0	20	
Patient C. H.* Test No. 1	6.3 (630%)	29.8 (39.7%)	105 (60%)	0.312 (10.4%)	4.54 (22.7%)	0.932
Test No. 2	7.0 (700%)	35.4 (47.1%)	99 (57%)	0.379 (12.6%)	8.85 (44.2%)	1.24
Diabetes Insipidus (Pituitary)				3.2	21	

\* Patient in a fasting state; no fluid during test and none for 2 hours before it.

Dr. John Talbott at the Massachusetts General Hospital, the sodium and potassium clearances were found to be normal.<sup>3</sup>

Special studies of renal function<sup>4</sup> were conducted to determine the chief site of impairment.\* The renal plasma flow was measured by the diodrast clearance and the glomerular filtration by the mannitol clearance. Diodrast and glucose were used to study, respectively, the maximal excretory and reabsorptive capacities of the tubules. There was shown to be a decrease in renal plasma flow without much change in glomerular filtration (table 4).

TABLE IV  
Special Renal Function Studies

	Normal	Patient C. H.	Diabetes Insipidus (Pituitary)*
Renal Plasma Flow, c.c./min.	697 ( $\pm 136$ )	450	480
Glomerular Filtration, c.c./min.	130 ( $\pm 20$ )	106	113
Filtration Fraction, %	19 ( $\pm 2$ )	23.6	26
Diodrast Tm, mg./min.	52 ( $\pm 9$ )	27.7	43
Glucose Tm, mg./min.	375 ( $\pm 79$ )	417.3	—

\* These data are taken from Winer.<sup>5</sup>

The resulting increase in the glomerular filtration fraction may imply that efferent arteriolar constriction exists. The maximal rate of glucose reabsorption (glucose Tm) was normal, while maximal tubular diodrast excretion (diodrast Tm) was reduced by about 50 per cent. These changes in renal function are similar to those found in diabetes insipidus of the "pituitary type," and are consistent with the pattern found in essential hypertension. Dissociation between glucose and diodrast Tm is frequently seen in the course of hypertensive disease, but not of the magnitude seen in this case. The marked impairment in the secretion of diodrast and phenol-sulphonphthalein is apparently due to impairment of active tubular excretion, but the normal glucose Tm indicates a normal mass of functioning proximal tubular tissue. This interpretation would explain the defect in water reabsorption which has led to continuous polyuria in this patient. In the course of the special studies the urine flow was observed to be between 14 and 28 c.c. per minute, which is about four times the volume in normal individuals under the same circumstances.

After making the foregoing observations an effort was made to study six other members of the family affected with diabetes insipidus. It was not

\* The authors are very grateful to Dr. Stanley Bradley of the Evans Memorial Hospital, Boston, who very kindly performed these tests and aided in interpreting the results.



possible to examine any of these patients, but some information, given below, was obtained from hospital records, from the patients or from their relatives.

*Patient M. R.* A clerk, aged 53, has been admitted to a veterans' hospital in Tuscaloosa, Alabama, on six occasions during the past 12 years. We are grateful to Dr. Dave Robertson for submitting to us the pertinent information that has been accumulated in this case. The patient stated that he had drunk an excessive amount of water since birth. The volume of his urine has been estimated many times and was found to average about 18 liters per day. He grew fairly well, but he has always been somewhat shorter than the average individual. He has had hyperorexia for many years, apparently eating a balanced diet with an average amount of salt. Occasionally he has severe diffuse headaches and feels dizzy and weak. The accumulated diagnoses are: diabetes insipidus, hypertrophic arthritis, blindness of right eye, corneal scar on the left eye, chronic otitis media, myocardial disease, complete atrophy of the right testicle, and chronic prostatitis. His height is 68 inches and he weighs 193 pounds. The hemoglobin determinations and the red blood cell counts were normal repeatedly. The examination of many specimens of urine revealed a specific gravity which varied from 1.000 to 1.003 and usually a neutral reaction. Albumin was sometimes present in small amounts and at other times none was found. Occasionally many white blood cells were present, but usually there were no formed elements in the urine. No glycosuria was ever found, but six fasting blood sugar estimations yielded values ranging from 105 to 147 mg. per 100 c.c. The concentrations in the blood of non-protein nitrogen, creatinine and urea nitrogen were normal. Eighty-five per cent of phenolsulphonphthalein injected intravenously was excreted in the urine within two hours. Two dilution and concentration (Mosenthal) tests revealed a maximal range in specific gravity of from 1.000 to 1.005. During these tests the patient developed circulatory collapse as a result of dehydration, and during one of them he became unconscious. Although he excreted only 724 c.c. of urine during one interval of 12 hours and 755 c.c. during another such period, the maximal specific gravity was 1.006.

Roentgenograms of the skull showed slight calcification in the region of the pineal body and the sella turcica was normal.

He was given 1 c.c. of pituitrin daily for four days, but there was no antidiuresis. However, he developed a marked febrile reaction following the last injection.

During the last 11 years his blood pressure has gradually risen from 115 to 160 systolic and from 84 to 106 diastolic.

*Patient R. L.* A veteran of the Army Air Force, aged 33, has been hospitalized for most of the past year with a urinary tract infection.

During the first month or two after birth it was observed that he drank an excessive amount of fluid and he urinated frequently. After a few years his symptoms largely disappeared, but he continued to drink as much as four quarts of water per day and got out of bed from one to three times per night to urinate.

His growth and development were normal. He had several examinations on entering the Air Force, but apparently no abnormalities were found. About one year ago he received an injury in the region of the left kidney on landing with a parachute. Since then he has not felt well. He was found to have dilation of his ureters and a urinary tract infection, which has not responded satisfactorily to prolonged treatment with penicillin and sulfonamides. The non-protein nitrogen has remained at about 70 to 100 mg. per 100 c.c. of blood. He has never received pituitrin therapy.

*Patient W. M.* A boy, 17 months of age, was apparently normal at birth. By the end of two months he stopped gaining weight, so breast feedings were discontinued and a formula was given. He became fretful and varied a great deal in his desires

for milk and water. At four months he developed a fever which rose to  $107^{\circ}$  within a few days. He was then taken to the University of Virginia Hospital, where many studies were conducted, a report of which was kindly supplied to us by Dr. William Waddell. Numerous urine examinations were made, but at no time was there any albumin, sugar, or cellular elements. The specific gravity varied from 1.006 to 1.010. The blood ureas were 45 and 37 mg. per 100 c.c. Numerous blood cultures were negative. The blood chloride was 655 mg. per 100 c.c.

In view of the uncertainty of the diagnosis, an exploratory operation was performed, but nothing remarkable was found; the kidneys seemed normal grossly. Two pyelograms, made after intravenous injection of the opaque medium, revealed normal appearing kidneys.

The amount of fluid ingested and excreted was not abnormal. Roentgen-rays of the chest, skull, long bones and sinuses showed nothing remarkable.

At six months of age he was taken to the Duke University Hospital, under the care of Dr. Wilbur C. Davison, who has supplied us with the pertinent information. The child's weight was only about one-half that of normal and he was 2.5 inches shorter than normal. There was generalized hypotonicity of all the muscles. There was slight fever and moderate leukocytosis. Urinalysis was negative, except for from one to three white blood cells per microscopic field. One blood culture and four urine cultures grew out a staphylococcus. The blood chemical studies revealed the following contents per 100 c.c.: phosphorus 3.6 mg., calcium 9.4 mg., non-protein nitrogen 45 mg., albumin 4.2 gm., globulin 3.5 gm. Many other studies failed to explain the child's illness.

He continued to have fever throughout the 45 days of his hospitalization, in spite of therapy with penicillin, staphylococcus antitoxin and streptomycin.

Soon after discharge from the Duke University Hospital, he began to drink excessive quantities of fluid and he developed polyuria. He drank 24 ounces of milk and 36 ounces of water daily. With a phenolsulphonphthalein test only a trace of the dye was excreted in the urine. The specific gravity of the urine was only 1.002, but after spraying pituitary powder in the nostrils it was 1.010 and it was thought that there was possibly some decrease in thirst and urine volume. This pituitary powder was used two or three times daily for about four months. On stopping this treatment no definite change in the polydipsia or polyuria was observed. His mouth always seemed to be dry and he never drooled saliva. At the age of one year the child weighed 13 pounds. At this time he could sit up, unsupported. At present the child is 17 months of age, weighs 15.7 pounds and ingests about 2,400 c.c. of fluid per day.

Not very much is known about the other three patients because they died many years ago. However, each of these individuals was a male and had polydipsia and polyuria which appeared soon after birth. One of the subjects died of kidney disease at the age of about 35. The causes of death in the other cases are not known; one of them died in infancy and the other one died during early adult life.

## DISCUSSION

It would seem probable that each of the seven individuals described had the same basic disease, but there apparently was a variation in the extent of the disturbance or in the patient's reaction to it. As seen in figure 1, the disease has appeared only in males, but has been transmitted only by females.

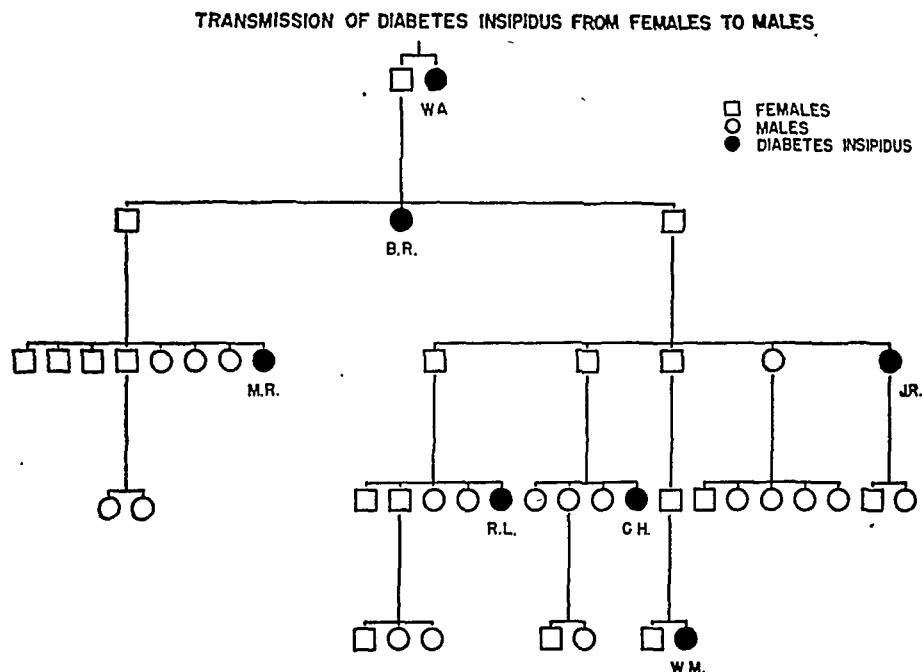


FIG. 1. This chart includes only members of the family that is affected with diabetes insipidus. There was no intermarriage in this group and no history of diabetes insipidus in their marital partners.

The manifestations of water imbalance appeared within the first few months of life. As long as an adequate supply of water was given, fairly satisfactory progress was made, although some retardation in growth occurred in all cases and two of the patients died early in life.

Marked restriction of fluid was found to produce pronounced thirst, irritability, depression, weakness and circulatory collapse. It is not surprising that such reactions should result when one considers the marked shift in water and electrolytes that occur. The ingestion of sodium chloride caused a moderate increase in thirst. On the other hand, several grams daily of potassium chloride given to one patient either had no effect or slightly decreased the quantity of urine. This patient noticed no definite effect from 20 mg. of desoxycorticosterone, or from 10 c.c. of adrenal cortical extract. None of three subjects treated with pitressin experienced a significant anti-diuretic effect. In one of these patients it was demonstrated that neither his serum nor his cells inactivated pitressin within 30 minutes. Since he responded to pitressin with generalized blanching of the skin and abdominal cramps, it was suspected that his kidneys were at fault. Renal function studies revealed an impairment in the renal plasma flow and in the tubular excretion of diodrast and phenols phosphthalein. The glomerular filtration was slightly decreased and the filtration fraction was slightly increased. There was a marked decrease in the sodium, potassium and creatinine clearances, and a moderate increase in the urea clearance. The patient excreted larger quantities of sodium and chloride within three hours after the intravenous infusion of normal saline than did a normal individual.

It seems likely that this patient has a physiological defect, and possibly a congenital malformation, in the loop of Henle and/or the distal convoluted tubules, thereby causing an inadequate reabsorption of water, as well as some of the other disorders of renal function mentioned in the previous paragraph. Moreover, it is presumable that a similar pathogenesis existed in the six relatives with "diabetes insipidus."

Four of the subjects had marked impairment of kidney function; in two it was not tested and in one the phenolsulphonphthalein excretion was normal. In the three subjects in which the blood pressure was estimated there was hypertension. In two individuals there was an increase in the fasting blood sugar and the brother of patient C. H. has diabetes mellitus, but not diabetes insipidus.

In analyzing the pathogenesis of diabetes insipidus, many factors must be considered, especially: (1) injury to the supraoptic nuclei, supra-optico-hypophyseal nerve tracts, or to the posterior lobe of the pituitary gland, (2) injury to the posterior portion of the hypothalamus, with particular reference to the nuclei of the tuber cinereum, and the mammillary bodies, and (3) anatomical or physiological defects in the tubules of the kidneys. On the basis of present data, which are incomplete, the clinical picture of patients with diabetes insipidus is similar in many respects regardless of the site of pathology. Moreover, the type of lesion has often remained occult. That there are variations in the characteristics of the syndrome is indicated by the many classifications that have been given.<sup>6,7</sup> Veil<sup>8</sup> divided the cases into two groups: (a) hyperchloremic-hypochloruric, and (b) hypochloremic-hyperchloruric. The former type is the one seen more commonly and is often due to a lesion in the diencephalon. The latter type has been produced experimentally by a lesion of the fourth ventricle. In the hypochloremic-hyperchloruric type pitressin is said to have no effect.<sup>9</sup> Biggart<sup>10</sup> reported three cases of diabetes insipidus which were refractory to pitressin. He observed lesions in the tuber cinereum and he suggested that damage to tuberal nuclei might result in diabetes insipidus which is not controlled by pitressin. Moreover, some of the cases with hereditary diabetes insipidus have failed to respond to the posterior lobe principle. In view of studies on the mechanism of pitressin,<sup>11</sup> it is difficult to see why such cases fail to respond to this hormone, unless there is a coexisting structural defect in the kidneys. In such cases there have not been a sufficient number of reports on the physiological reactions and histological appearances of the kidneys to determine whether they contain the significant abnormality. To be sure, it is well known that polyuria may be associated with kidney disease and in some instances of tubular damage there may be such a marked loss of water and salt that a state of vascular collapse results. These patients usually do not excrete more than four or five liters of urine per day and they have a marked impairment of renal function in many respects. However, an abnormality in the loop of Henle is conceivable, which would impair reab-

sorption of water and which might not affect other renal functions to a significant extent. A congenital absence of the loop of Henle would seem possible since, phylogenetically, it was the last segment of the nephron to be added. It is present in birds and mammals, but is absent in frogs, fish and alligators. Moreover, the latter species of animals do not have a significant antidiuretic response to pitressin.<sup>12</sup> Since these lower animals possess all of the segments of the nephron except the loop of Henle, there is a possibility that the facultative reabsorption of water<sup>13</sup> that occurs in birds and mammals takes place in the loop of Henle, against osmotic gradients, as the result of a specific action by pitressin.

Therefore, it appears feasible to assume that in the cases reported above there was a congenital defect in the loop of Henle, as well as in the distal convoluted tubules, but the glomerular and proximal convoluted tubular functions were essentially normal.

Many cases of hereditary diabetes insipidus have been reported.<sup>6</sup> This entity is more common in boys, usually responds satisfactorily to pitressin and has not been known to be associated, etiologically, with kidney disease. Males and females have transmitted the disease. In general, hereditary diabetes insipidus has not markedly reduced life expectancy.

### SUMMARY

Seven members of one family, in five generations, were the victims of diabetes insipidus. The disease made its appearance soon after birth. It occurred only in males, was transmitted only by females, and appeared to be a sex-linked, recessive characteristic. It did not respond to pitressin therapy. The disease led to some impairment of growth and two of the individuals died early in life.

Neither the serum nor the body cells were found to inactivate pitressin any more rapidly than in normal individuals. Since one patient was observed to react to pitressin with generalized blanching and abdominal cramps, but not with a decreased polyuria, it was concluded that a physiological, and possibly an anatomical, defect in the kidneys existed. Renal function studies in this patient showed impairment in the renal plasma flow and in the tubular excretion of diodrast and of phenolsulphonphthalein. There was also a decrease in the plasma clearance of urea, sodium, potassium and creatinine. There was a slight decrease in the glomerular filtration and increase in the filtration fraction. The maximal rate of tubular glucose reabsorption was normal. Sodium chloride administered intravenously was excreted fairly rapidly. It is concluded that there probably is a congenital anomaly of the loop of Henle and the distal convoluted tubules. Although an opportunity of conducting similar renal function studies in other cases did not exist, it seems likely that they had the same type of disease. No previous reports of this syndrome have been found, although it is probable that it has existed.

## BIBLIOGRAPHY

1. HAM, G. C., and LANDIS, E. M.: Comparison of pituitrin with antidiuretic substance found in human urine and placenta, *Jr. Clin. Invest.*, 1942, xxi, 455.
2. GILMAN, A., and GOODMAN, L. S.: The secretion of an antidiuretic hypophyseal hormone in response to the need for renal water conservation, *Science*, 1936, lxxxiv, 24.
3. TALBOTT, J. H.: Personal communication.
4. GOLDRING, W., and CHASIS, H.: Hypertension and hypertensive disease, 1944, The Commonwealth Fund, New York.
5. WINER, N. J.: Renal function in diabetes insipidus, *Arch. Int. Med.*, 1942, lxx, 61.
6. WARKANY, J., and MITCHELL, A. G.: Diabetes insipidus in children, *Am. Jr. Dis. Child.*, 1939, lvii, 603.
7. TALBOTT, J. H.: Diabetes insipidus, *Nelson Loose-Leaf Medicine*, 1941, 49.
8. VEIL, W. H.: Ueber die Wirkung gesteigerter Wasserzufuhr auf Blutzusammensetzung und Wasserbilanz: Beitrag zur Kenntnis der Polydipsie und des Diabetes insipidus, *Deutsch. Arch. f. klin. Med.*, 1916, cxix, 376.
9. BERNARD, C.: *Leçons de physiologie expérimentale appliquée à la médecine*, 1855, J.-B. Bailliere, Paris.
10. BIGGART, J. H.: Anatomic basis for resistance to pituitrin (posterior pituitary preparation), *Jr. Path. and Bact.*, 1937, xlv, 305.
11. VERNEY, E. B.: The secretion of pituitrin in mammals, as shown by perfusion of the isolated kidney of the dog, *Proc. Roy. Soc. London*, s.B. 1926, lxxxxix, 487.
12. BURGESS, W. W., HARVEY, A. M., and MARSHALL, E. K., JR.: The site of the antidiuretic action of pituitary extract, *Jr. Pharmacol. and Exper. Therap.*, 1933, xlix, 237.
13. SMITH, H. W.: *The physiology of the kidney*, 1937, Oxford University Press, New York.

# NON-HEMOPHILIC HEREDITARY HEMORRHAGIC DIATHESIS: REPORT OF A FAMILY OF BLEEDERS \*

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IN 1926 von Willebrand<sup>1</sup> described a familial bleeding tendency affecting both sexes and characterized by a prolonged bleeding time, accompanied by a normal coagulation time and platelet count. Prior and subsequent to this report there appeared many descriptions of atypical hemorrhagic diatheses. Glanzmann<sup>2</sup> and others<sup>3,4</sup> described an hereditary bleeding tendency, appearing in persons of both sexes, whose blood exhibited deficient clot retraction with a normal bleeding time, clotting time, and number of platelets. Buckman<sup>5</sup> investigated a familial hemorrhagic diathesis affecting males and females who had a prolongation of their bleeding and clotting times. A family of male and female bleeders with prolonged clotting times and normal bleeding times and platelet counts was reported by Handley and Nussbrecher.<sup>6</sup> A similar case was recently studied by Madison and Quick.<sup>7</sup> Curschmann<sup>8</sup> has described two families with frequent attacks of epistaxis occurring in both sexes, in the absence of hematologic abnormalities. A family with a similar hereditary bleeding tendency and normal blood findings was investigated recently by Evans and MacLaren.<sup>9</sup> Lombard,<sup>10</sup> Müller,<sup>11</sup> and others<sup>12, 13, 14, 15</sup> have investigated microscopic changes occurring in the capillaries of the nailbeds in various hemorrhagic diatheses. Since von Willebrand's reports<sup>16</sup> there have appeared numerous other descriptions of a similar hereditary hemorrhagic diathesis affecting males and females.<sup>17 through 23</sup>

We have recently studied a family of bleeders who present findings resembling those of von Willebrand's cases. The family tree is shown in figure 1. Of the 62 members, 12 males and eight females are affected. Both sexes have the bleeding tendency, and either may transmit it. Although it has been suggested that this disease is inherited through a dominant sex-linked character residing in the x chromosome, the transmission from father to son, as occurred in our cases and other reported families, would tend to exclude such a mode of inheritance.

The pertinent clinical data are presented in table 1. The age of the patients when initial symptoms appeared varied from four months to 40 years, with most patients experiencing onset of symptoms during childhood. There was a tendency toward a diminution in the bleeding episodes as the patients grew older, with the exception of one individual (number 16) in whom the bleeding persisted throughout life. All of the affected patients had bled for

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prolonged periods of time following minor degrees of trauma. Fifteen of the 20 patients had frequent episodes of epistaxis. Four of the eight females experienced excessive menstrual bleeding, and two had post-partal hemorrhages. Prolonged bleeding following tooth extractions occurred in four cases. Two patients had bleeding from the site of incision following appendectomy, and one patient had repeated hemorrhages following tonsillectomy. Bleeding from the gastrointestinal tract was noted in three cases. Pulmonary hemorrhages occurred in four cases. One patient experienced hematuria; a complete genito-urinary investigation revealed no pathology. Neither petechiae nor a palpable spleen were found in any of the five patients that were examined by us.

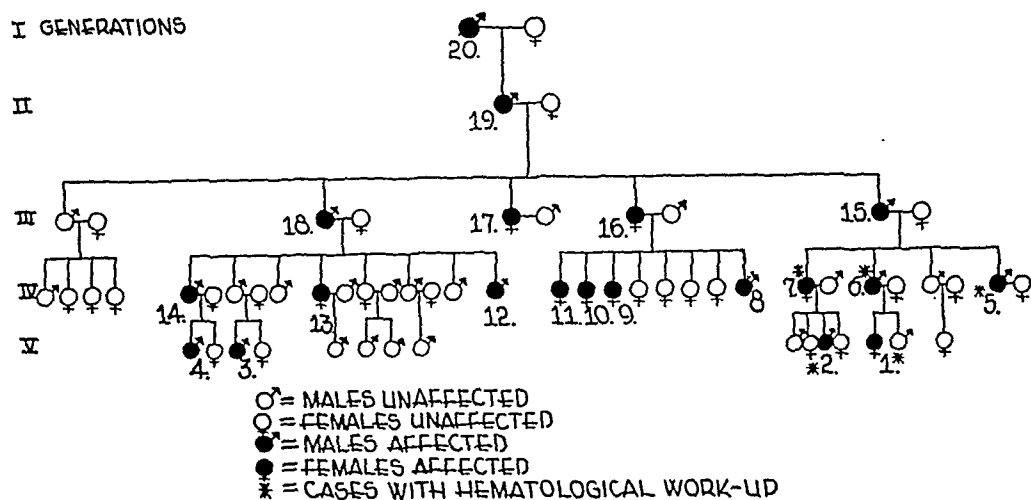


FIG. 1.

Hematological findings in the five cases studied are presented in table 2. The coagulation times of whole blood and recalcified plasma after low and high speed centrifugation, clot retraction, prothrombin time, platelet count, serum calcium, and capillary resistance were within normal limits. Bone marrow studies on one patient (number 5) revealed no abnormalities. An erythrocyte fragility test performed on the same patient was normal. Bleeding times were repeatedly determined at varying intervals, and prolongation occurred in four of the five cases. The bleeding time varied in the same individual from week to week. During periods when symptoms were present, it was usually increased. One patient (number 6) was never observed during an episode of bleeding. His bleeding time was four minutes.

Microscopic studies of the capillaries in the nailbeds of the fingers were made in three of the patients. Although a uniform picture was not observed in all of the capillaries studied, some of the capillaries in each patient's nailbeds revealed tortuosity of the capillary loops and failure of the blood cell columns to disappear after injury, the column remaining visible and terminating in the small area of extravasated blood. Abnormalities of the



TABLE I  
Clinical Data

Patient*	Sex and Age	Age at Onset of Bleeding		Treatment	Cause of Death
1	F 17 yrs.	10 yrs.	Epistaxis; gums. Menorrhagia (18-21 days). Cut tongue and bled 6 hrs. Prolonged bleeding following minor trauma.	Local**	Living
2	M 12 yrs.	4 mos.	Rectal hemorrhage for 24 hrs. at age of 4½ mos. Epistaxis; gums. Bled for 24 hrs. following tooth extraction. Prolonged bleeding following minor trauma.	Transfusions and local	Living
3	M 12 yrs.	3 yrs.	Gums; epistaxis. Bled for 3 days after tonsillectomy. Prolonged bleeding following minor trauma.	Transfusions and local	Living
4	M 3 yrs.	7 mos.	Cut mouth at age of 7 mos. and bled for 20 days. Epistaxis; gums. Prolonged bleeding following minor trauma.	Transfusions and local	Living
5	M 44 yrs.	Childhood	Epistaxis. Gums. Hemoptysis. Melena. Hematuria. Prolonged bleeding following minor trauma.	Transfusions and local	Living
6	M 40 yrs.	25 yrs.	Epistaxis. Gums. Following appendectomy bled from incision for 48 hrs. Following tooth extraction bled for 72 hrs. Prolonged bleeding following minor trauma.	Transfusions and local	Living
7	F 38 yrs.	16 yrs.	Epistaxis. Gums. Following tooth extraction bled 48 hrs. Menorrhagia (18-20 days). Bled excessively during and following appendectomy. Post-partial hemorrhage (5-7 days) with each child. After giving transfusion bled 36 hrs. from needle puncture site. Prolonged bleeding following minor trauma.	Transfusions and local	Living
8	M Died	Childhood	Gums. Prolonged bleeding following minor trauma.	Local	Bled to death following gunshot wound of arm
9	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 25 yrs.

\* Number refers to numbers in figure 1.

\*\* Packing nose; pressure bandage, etc.

TABLE I (Continued)

## Clinical Data

Patient*	Sex and Age	Age at Onset of Bleeding		Treatment	Cause of Death
10	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 30 yrs.
11	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 25 yrs.
12	M 20 yrs.	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Local	Living
13	F 33 yrs.	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Local	Living
14	M 35 yrs.	Childhood	Epistaxis.	Local	Living
15	M Died	40 yrs.	Epistaxis. Gums. Bled for 36 hrs. following tooth extraction. Melena (10-15 times). Bled for 72 hrs. following small cut on forearm. Prolonged bleeding following minor trauma.	Local	Heart attack at 52 yrs.
16	F Died	Childhood	Menorrhagia and post-partal hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Uterine hemorrhage (post-partal) at 45 yrs.
17	F Died	Childhood	Epistaxis. Menorrhagia (10-12 days). Prolonged bleeding following minor trauma.	Local	Cancer of uterus at 35 yrs.
18	M Died	Childhood	Epistaxis. Gums. Prolonged bleeding following minor trauma.	Local	"Heart trouble" at 55 yrs.
19	M Died	Childhood	Epistaxis. Gums. Hematemesis. Melena. Prolonged bleeding following minor trauma.	Local	Cause of death unknown, at 97 yrs.
20	M Died	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Unknown	Unknown

capillaries have been seen in patients with mental deficiencies,<sup>34</sup> hypertension, hypotension, nephritis, diabetes, Raynaud's disease, acrocyanosis, clubbing of the fingers, and a variety of other conditions.

Treatment in this family consisted of local measures such as nasal packing, pressure bandages, and application of fibrin foam. Transfusions were

TABLE II  
Blood Work

	1	2	5	6	7
Patient*	1	2	5	6	7
RBC (millions/cu.mm.)	4.5	5.0	3.4	4.5	4.7
Hemoglobin (gm. %)	12.9	14.2	11.0	13.6	14.6
Hematocrit (%)	41	45	28	42	43
WBC (cu.mm.)	5,000	4,600	5,700	6,100	6,200
Polys (%)	68	61	80	70	78
Lymphocytes (%)	26	38	19	28	21
Eosinophiles (%)	0	1	—	1	1
Monocytes (%)	6	0	1	1	—
Platelets (cu.mm.)	450,000	210,000	230,000	210,000	164,000
Prothrombin Time—Quick <sup>34</sup> (% normal)	88	94	100	98	90
Bleeding Time—Duke <sup>35</sup> (min.)	8-10	4-16	4-14	4	13-22
Whole Blood—Lee and White <sup>36</sup> (min.)	3	5	6	4.5	3
Recalcified Plasma Slow Centrifugation <sup>37</sup> (sec.)	90	94	100	94	92
Recalcified Plasma High Speed Centrifugation <sup>37</sup> (sec.)	96	98	112	105	108
Clot Retraction	Start—1 hr.	Start—2 hrs.	Start—1½ hrs.	Start—2 hrs.	Start—3 hrs.
Rumpel-Leede Tourniquet Test	Complete—24 hrs.	Complete—24 hrs.	Complete—24 hrs.	Complete—24 hrs.	Complete—24 hrs.
Serum Calcium (mg. %)	Negative	Negative	Negative	Negative	Negative
	11.4	11.5	10.5	10	10

\* Number refers to number on chart of family tree.

given during many of the episodes with questionable result as regards control of bleeding.

Five members of the family are known to have bled to death, three of pulmonary hemorrhage, one following a gunshot wound, and one of uterine bleeding. We did not have the opportunity to investigate these patients; the relative rôles of the bleeding tendency and of unrelated pathology in causing death are therefore not known.

### SUMMARY

The literature on non-hemophilic hereditary hemorrhagic diatheses is briefly summarized. A hereditary hemorrhagic diathesis affecting 20 members of a family during five generations was investigated. Both sexes were affected and either was capable of transmitting the bleeding tendency. These patients exhibited prolonged bleeding following minor trauma, with the majority experiencing epistaxis and bleeding from the gums. Bleeding from the lungs, gastrointestinal tract, urinary bladder, and uterus was also observed. Prolonged bleeding following tooth extraction, tonsillectomy, and appendectomy occurred. The only abnormal hematologic findings were a prolonged bleeding time and changes in the capillaries of the nailbeds of the fingers. Treatment consisted of local measures and transfusions. Four members died following pulmonary and uterine hemorrhages; we did not have the opportunity to investigate these patients.

I am greatly indebted to Dr. Johan T. Peters for his translation of the foreign journals.

### BIBLIOGRAPHY

1. VON WILLEBRAND, E. A.: Hereditäre Pseudohemofiele, *Finska Läkaresällskapets Handlingar*, 1926, lxxviii, 87.
2. GLANZMANN, E.: Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen, *Jahrb. Kinderheilk.*, 1918, lxxxix, 1.
3. KROMEKE, F.: Zur Frage der hereditären hämorrhagischen Diathese (Thrombasthenie), *Deutsch. med. Wchnschr.*, 1922, xlviii, 1102-1105.
4. VAN DER ZANDE, F.: Pseudohemophilia, *Nederl. Tijdschr. v. Geneesk.*, 1923, i, 544-553.
5. BUCKMAN, T. E.: Atypical pathological hemorrhage in early life, *Am. Jr. Med. Sci.*, 1928, clxxv, 307-312.
6. HANDLEY, R. S., and NUSSBRECHER, A. M.: Hereditary pseudohemophilia, *Quart. Jr. Med.*, 1935, iv, 165-178.
7. MADISON, F. W., and QUICK, A. J.: Hemophilia-like disease in the female, with a note on the clotting time of recalcified plasma, *Am. Jr. Med. Sci.*, 1945, ccix, 443-447.
8. CURSCHMANN, H.: Über familiäres Nasenbluten als Ausdruck einer Pseudohämophilie, *Klin. Wchnschr.*, 1930, ix, 677.
9. EVANS, R. W., and MACLAREN, H. C.: Hematuria associated with haemorrhagic diathesis, *Lancet*, 1945, ii, 175.
10. LOMBARD, W. P.: *Am. Jr. Physiol.*, 1911, xxix, 335.
11. MÜLLER, O.: Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen, 1922, Ferdinand Enke, Stuttgart.
12. WRIGHT, I. S., and DURYEE, A. W.: Human capillaries in health and in disease, *Arch. Int. Med.*, 1933, lii, 545-572.

13. LEADER, S. D.: Capillary microscopy in children, *Am. Jr. Dis. Child.*, 1932, xlv, 403-416.
14. MACFARLANE, R. G.: Critical review: The mechanism of haemostasis, *Quart. Jr. Med.*, 1941, x, 1-29.
15. DAVIS, E.: Capillary microscopy with special reference to capillary petechiae, *Am. Jr. Med. Sci.*, 1946, ccxii, 192-196.
16. VON WILLEBRAND, E. A.: Über hereditäre Pseudohämophilie, *Acta. med. Scandinav.*, 1931, lxxvi, 521.
17. GEIGER, A., and EVANS, E. G.: Atypical hereditary hemorrhagic syndromes, *Internat. Clin.*, 1938, ii, 135-157.
18. ROSLING, E.: Über hereditäre hämorrhagische Diathesen, *Acta med. Scandinav.*, 1926, lxxii, 104.
19. ROTHMAN, P. E., and NIXON, M. K.: Familial purpura hemorrhagica without thrombopenia, *Jr. Am. Med. Assoc.*, 1929, xciii, 15-17.
20. FARBER, J. E.: A familiäl hemorrhagic condition simulating hemophilia and purpura hemorrhagica, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 815-822.
21. FOWLER, W. M.: Hereditary pseudo-hemophilia, *Am. Jr. Med. Sci.*, 1937, cxciii, 191-198.
22. BRUUN, E.: Hereditary hemorrhagic diathesis, *Acta. med. Scandinav.*, 1939, cii, 639-648.
23. LITTLE, W. D., and AYRES, W. W.: Hemorrhagic disease; familial bleeding tendency of unusual type with splenomegaly affecting and transmitted by both males and females, *Jr. Am. Med. Assoc.*, 1928, xci, 1251-1252.
24. KENNEDY, R. L. J.: Diseases of children benefited by splenectomy, *Jr. Am. Med. Assoc.*, 1928, xci, 874-878.
25. SCHLICKE, C. P., and HALL, B. E.: Hereditary pseudohemophilia, *Proc. Staff Meet. Mayo Clin.*, 1938, xiii, 529-533.
26. BAIN, C. G.: Hereditary pseudohemophilia, *Northwest Med.*, 1939, xxxviii, 221-223.
27. SMITH, L. A., and WATKINS, C. H.: Gastric hemorrhage with hereditary pseudo-hemophilia. Report of a case, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 589-591.
28. WEEKS, E.: Familial bleeding. Report of two cases, *Am. Jr. Dis. Child.*, 1934, xlvii, 1318-1322.
29. BAILEY, F. R., and McALPIN, K. R.: Familial purpura. Report of two cases, *Am. Jr. Med. Sci.*, 1935, cxc, 263-268.
30. GIFFIN, H. Z.: Unusual types of hemorrhagic diseases, *Am. Jr. Med. Sci.*, 1928, clxxv, 44-49.
31. MINOT, B. R.: A familial hemorrhagic condition associated with prolongation of the bleeding time, *Am. Jr. Med. Sci.*, 1928, clxxv, 301-306.
32. PERKINS, W.: Pseudohemophilia: Case study, *Blood*, 1946, i, 497-504.
33. ESTREN, S., SANCHEZ MEDAL, L., and DAMESHEK, W.: Pseudohemophilia, *Blood*, 1946, i, 504-533.
34. POWDERMAKER, F.: Capillary forms in relation to certain problems in development, *Arch. Neurol. and Psych.*, 1929, xxii, 1207-1210.
35. QUICK, A. J.: The clinical application of the hippuric acid and the prothrombin tests, *Am. Jr. Clin. Path.*, 1940, x, 222-223.
36. DUKE, W. W.: The relation of blood platelets to hemorrhagic disease; description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion, *Jr. Am. Med. Assoc.*, 1910, lv, 1185-1192.
37. LEE, R. I., and WHITE, P. D.: A clinical study of the coagulation time of blood, *Am. Jr. Med. Sci.*, 1913, cxlv, 495-503.
38. QUICK, A. J.: The diagnosis of hemophilia, *Am. Jr. Med. Sci.*, 1941, cci, 469-474.

## EXPERIENCES WITH TYROTHRIN IN RHINOLOGY, SURGERY AND DERMATOLOGY \*

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IN the enthusiasm with which the medical profession has accepted and used penicillin as a chemotherapeutic agent, another antibiotic substance of considerable antibacterial activity has not received the full consideration it deserves. Although tyrothricin does not possess the broad application of penicillin because it cannot be administered systemically, this drug has a definite place in the treatment of surface infections. One of the great problems which lies ahead for the medical profession will be the accurate appraisal of the various chemotherapeutic and antibacterial agents available for different infections. In the treatment of mucous membrane and skin infections and surface wounds, tyrothricin warrants trial because in some instances the offending pyogenic cocci are either more sensitive to tyrothricin than to penicillin or even resistant to penicillin and sensitive to tyrothricin. In addition, tyrothricin possesses the particular advantage of stimulating the formation of granulation tissue and epithelium.

Of special interest in connection with this subject is a recent report on the effective use of Gramicidin S in 1,500 cases in 10 leading Soviet hospitals.<sup>1</sup> The cases treated comprised the following groups: (1) suppuration of soft tissues, (2) preparation for skin grafting, (3) osteomyelitis, (4) empyema and peritonitis, (5) skin infections and (6) prophylactic use. Gramicidin S exhibits certain chemical and biologic properties different from those of the gramicidin of Dubos (tyrothricin is the parent substance from which gramicidin is derived), but evidently possesses similar antibacterial action.

Tyrothricin, discovered by Dubos in 1939,<sup>2</sup> is an antibiotic prepared from cultures of *Bacillus brevis* by extraction of the autolyzed culture with acid alcohol and precipitation of the active material from the alcoholic solution by large volumes of saline.

Tyrothricin as available commercially is a mixture of two crystalline products, gramicidin and tyrocidine. Both of these substances are polypeptides insoluble in water in the presence of electrolytes. Both exhibit antibacterial activity in vitro; tyrocidine, however, behaves like a cationic detergent and loses most of its activity in the presence of animal tissues and fluids. Gramicidin, on the contrary, retains its antibacterial activity in the presence of serum proteins and is therefore effective in vivo. Thus, it is gramicidin which is responsible for the therapeutic effects and which exerts

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a selective bacteriostatic and bacteriocidal effect against Gram positive cocci, gonococci and meningococci, diphtheria and diphtheroid bacilli, aerobic and anaerobic sporulating bacilli, etc., but is inactive against Gram negative bacilli.

Unfortunately, gramicidin is hemolytic and therefore cannot be introduced by the intravenous route. On the other hand, it has little or no toxic effect on other cells as exemplified by its lack of toxic action in tissue cultures. This has permitted the use of tyrothricin and gramicidin on a large scale in the treatment of bovine mastitis,<sup>3</sup> an infection of the udder caused by Group B streptococci. (The drug is injected directly through the teat canal into the infected udder.)

The alcoholic solution of tyrothricin is completely stable and can be kept for any length of time. Tyrothricin can be procured commercially in a 2 per cent alcoholic solution and the desired final concentration can be obtained by diluting with sterile distilled water. Electrolytes, such as sodium chloride, cannot be used as diluents because they cause precipitation of the material.

The 2 per cent alcoholic solution of tyrothricin \* was used in this series, except in the very early rhinologic cases. In the early rhinologic cases, an alcoholic solution was prepared by one of us (J. L. G.) from the desiccated form of tyrothricin.†

The diluted tyrothricin was kept in the refrigerator and used only within the first five days after the preparation of the dilution. Usually fresh material was prepared every two to three days. The concentration of tyrothricin used in these cases was 0.2 mg. per cubic centimeter (1:5,000), e.g., 1 c.c. of a 2 per cent alcoholic solution of tyrothricin was added to 100 c.c. distilled water. This concentration had been found most effective in the treatment of bovine mastitis.

This study describes four separate investigations to determine the general effectiveness of tyrothricin in limited groups of (1) rhinological infections, (2) postoperative pilonidal cyst wounds, (3) minor surgical infections and (4) infectious dermatoses. Infections of the nasal mucous membrane, open and skin wounds were available for study at AAF Regional Station Hospital, Drew Field, Florida, from January 1943 to August 1944. The treatment of sinus infections described in Section I below was carried out on a small number of patients at The Mount Sinai Hospital, New York, prior to September 1942 through the coöperation of Dr. E. B. Schoenbach.

## I. OBSERVATION ON THE EFFECTS OF TYROTHRIN IN RHINOLOGY

(Lt. Colonel Joseph L. Goldman, MC)

In the field of rhinology, tyrothricin was employed in three types of cases: (1) the treatment of sinus infections, (2) direct and prophylactic treatment

\* Supplied by Parke, Davis and Company, Detroit, for investigative study.

† Supplied by Dr. Dubos and Wallerstein Co., New York, for investigative study.

of postoperative sinus wounds and sinuses and (3) the prophylactic treatment of acute coryza to prevent or reduce the severity of the suppurative state.

Tyrothricin is effective in clearing quickly many acute infections of the maxillary antrum which are caused by pyogenic cocci sensitive to tyrothricin. It was not unusual to see an acute infection cured after one or two instillations of tyrothricin into the sinus. Thirty antral infections have been treated with tyrothricin during the past four years with favorable results. These infections were caused by hemolytic streptococci, pneumococci and *Staphylococcus aureus*. After washing out an antrum with warm normal saline solution, sufficient tyrothricin 1 : 5,000 was instilled to fill the antrum. The head was kept in a horizontal position for at least 15 minutes.

In my experience the instillation of tyrothricin has had no influence on chronic infections of the sinuses. If tyrothricin is instilled frequently into a chronically infected antrum, it may be difficult to isolate the causative microorganisms for a few days after the instillation. From the absence of curative effect one can deduce that tyrothricin acts only on the very surface and does not penetrate the deeper layers and glands of the diseased mucous membrane.

My experience in the postoperative treatment of antrums and ethmoidal areas has been limited but sufficient to impress me with the value of tyrothricin in these cases. In five intranasal antrotomies (three *Staphylococcus aureus*, two *Streptococcus hemolyticus*) the antrum was packed with gauze saturated with 1 : 5,000 tyrothricin and the gauze was kept moist with tyrothricin for 24 hours. This was followed by the instillation of tyrothricin into the antrum at first daily (three to four days) and then every other day (four to six days). In three instances of intranasal sphenoethmoidectomy and antrotomy, the area operated upon was packed for 24 hours with gauze saturated with tyrothricin 1 : 5,000 and then kept moist. Three cases of polypectomy and two cases in which the anterior tip of the middle turbinate and anterior ethmoidal cells were removed were treated postoperatively in a similar fashion. Beneficial effect was observed in every instance. The reaction of the tissues in the operated areas was considerably less than usually occurs. The areas exhibited very little or no exudate or polypoid swelling. The antrums, by comparison with past experience, also cleared more quickly.\*

Crowe and his associates<sup>4</sup> have reported similar experiences with tyrothricin in these types of cases. Their method for determining the sensitivity of microorganisms to tyrothricin was used in the above cases.

The application of tyrothricin in the attempt to prevent the suppurative stage of the acute coryza has been especially gratifying. The use of bacteriocidal and bacteriostatic agents for this purpose has a bacteriologic rationale. Studies on the bacterial flora of the nose and nasopharynx made by me at The

\* The writer has used penicillin 500 units per c.c. in subsequent intranasal operations and has not found this antibiotic superior to tyrothricin.



Mount Sinai Hospital, New York,<sup>5</sup> and at AAF Regional Station Hospital, Drew Field, Florida,<sup>6</sup> showed that only a small number of microorganisms of the non-pathogenic variety inhabit the normal nose (previously also reported by Jacobson and Dick<sup>7</sup> in a significant study), while pathogenic bacteria exist in the nasopharynx. These microorganisms, I believe, gain entry into the nose when the antibacterial defenses of the nose are inhibited during the virus phase of the acute coryza.

Ebert<sup>8</sup> was successful in lessening the severity of the acute coryza by spraying the nose at regular intervals with sulfathiazole powder. Schoenbach and associates were able to eliminate the *Streptococcus hemolyticus* from the rhinopharynx of carriers by using tyrothricin.

Forty patients were carefully selected for this prophylactic therapy. These consisted chiefly of members of the hospital staff at Drew Field and their families. Only patients with the history that they developed either a severe or protracted suppurative stage were given the treatment. An equal mixture of tyrothricin 1:5,000 and neosynephrin 1 per cent was administered in the first half of the cases and an equal mixture of tyrothricin 1:5,000 and privine 0.1 per cent in the second half of the series (neosynephrin ½ per cent and privine .05 per cent were employed for children and patients with pronounced vasomotor mucous membrane). Beginning with the first day of the acute coryza in most of the cases and the second day of the remaining cases, the nose was sprayed every two hours, except during sleep, in adequate amount for the solution to reach the nasopharynx. In 22 cases the suppurative stage was prevented, in 13 the suppurative phase of the acute coryza was greatly reduced in amount and duration and in five no effect was noted. The first two groups of patients were very pleased with the results.

## II. OBSERVATIONS ON THE EFFECTS OF TYROTHRIN IN POSTOPERATIVE PILONIDAL CYST WOUNDS

(Captains S. A. Roddenberry, MC, and M. P. Rizzuto, MC)

This is a report of clinical observations on the effect of tyrothricin on wound healing. The wounds studied were those following surgical treatment of pilonidal cysts of the sacrococcygeal area. This is not intended to be a discussion of the treatment of pilonidal cysts. These wounds being available for study, tyrothricin was employed in an effort to find a more suitable agent than those commonly used to promote rapid, healthy healing of stubborn wounds.

Daily morning dressings were done on all wounds studied. A fine mesh sterile gauze packing, saturated with 1:5,000 tyrothricin, was employed. Dressings were kept moist with tyrothricin irrigations every four hours. (On three cases in which penicillin solution was used, a similar technic was employed, with 500 Oxford Units of penicillin per c.c. of distilled water.)

For the purpose of reporting, cases are divided into four main groups:

1. Open wounds resulting from excision of pilonidal cysts and sinuses. This group also included excision of recurrent pilonidal cysts and excision of pilonidal cyst wounds resulting from breakdown of pilonidal cyst scars. All of these wounds following surgery were of a similar type and varied chiefly in size and shape.

2. Open wounds resulting from infection and breakdown following primary closure after excision of pilonidal cyst. When gross infection was recognized in any wound, all sutures were removed and the wound was opened and packed.

3. Abscess cavities resulting from incision and drainage of sacrococcygeal abscesses. Included in this group were cases of abscess formations which were of known pilonidal cyst origin, manifested by the presence of sinus openings, fistulous tracts and hair. Included, also, were cases in which this evidence was lacking but in which a presumptive diagnosis of pilonidal cyst was made because of the typical location and appearance of the abscess.

4. Miscellaneous cases which included a heterogeneous group of pilonidal cyst wounds. This group embraced minor wound complications following excision and primary closure such as slight separation of skin edges, stitch abscess and breakdown of previously healed wound with separation of wound margins.

*Material.* In Group I there were 29 cases, 15 of which were treated with tyrothricin alone, employing the technic described above.

The granulations of these wounds assumed a smooth salmon pink to cherry red color. As a rule, these granulations bled easily on pressure, were painless to touch and presented only slight mucoid drainage on the dressing. The amount of drainage from these wounds was minimal in comparison with previous wounds treated with other substances. Healing was more rapid and the margins of the wounds, characteristically, were surrounded by a bluish-white film of epithelium growing centripetally and attaching itself firmly to the granulations in its progress. Measurements of the wounds were taken periodically in an effort to record the actual rate of healing and the total healing time. This policy was soon abandoned because the variation in size and contour of wounds made accurate measurements impossible. Healing time was tabulated but due to the multiplicity of uncontrollable and variable factors between individual wounds, a detailed statistical report is not being offered. This seemed to us to be invalid and misleading. In general, healing was enhanced in this group and the wounds maintained a healthy, clean appearance throughout.

In six cases penicillin was employed and a similar technic followed. Penicillin was used locally in a 500 unit per c.c. solution for 20 days on these cases. Because of an acute shortage of penicillin, the treatment was completed with tyrothricin. Clinically the wounds under the influence of penicillin reacted in a manner similar to those in which tyrothricin was used alone. Healing was rapid and no significant change in the rate of healing

was noted following the shift from penicillin to tyrothricin. It was observed that in wounds under the influence of penicillin there was a greater amount of mucoid drainage on the dressing than in those in which tyrothricin was used. Also, the wounds treated with penicillin lacked the healthy appearance noted in the cases treated with tyrothricin and granulations exhibited a paler appearance. Dressings in the cases treated with penicillin were accompanied by more pain for the first postoperative week.

In eight cases various other substances were used. Plain saline packing was employed in two cases. These granulating wounds presented considerable mucopurulent drainage and were more sensitive to the touch for the first four days. The granulations were pale and did not bleed easily. Healing progressed rather slowly when compared with the above cases.

Three cases received azochloramide packing. The granulations were similar to those in which saline was employed. After using this solution for two and one-half weeks, one case developed urticaria and the treatment was discontinued. Patch test was positive in this case.

In one case vaseline gauze packing was used. Exudation and drainage were marked in this wound. The granulations remained pale and rather sensitive to the touch throughout the treatment. Healing was slow.

In two cases vaseline gauze, sprinkled with sulfanilamide powder, was used. The exudation seemed to be less and the granulations appeared healthier than in the last case. But healing progressed slowly as compared with the tyrothricin cases.

*In Group II* there were seven cases. All these cases had primary closure of the wound after excision of the pilonidal cyst and sinus. Cotton sutures were used in all cases. Ranging from the third to fifth postoperative day, the wounds became infected and were accompanied by pain, a rise in temperature and in three cases by a foul discharge. All these wounds were grossly infected. The sutures were removed, the wounds opened and packed with tyrothricin in the manner previously described. Within 24 to 48 hours, drainage ceased and the wounds assumed a clean, healthy appearance, and healed rapidly, maintaining the characteristics of the tyrothricin-treated wounds described in Group I.

*In Group III* there were 21 cases. Tyrothricin was used in the treatment of all the patients in this group. This was the group of acute abscess of the sacrococcygeal area. These cases were treated by incision and drainage. The pus evacuated was typically of a thick granular nature, foul smelling and was indicative of marked tissue destruction. The cavities varied in size but were usually large. These wounds were treated with tyrothricin in the routine manner. The effect of tyrothricin in this group of cases was very good. The wounds healed by granulation and the appearance of the wound surface was the same as in the cases described in Group I.

There were five cases *in Group IV*. The wounds were all small, varying from the size of a navy bean to a buckshot. These wounds were small areas

of separation of previously healed wounds, overlapping of skin edges and small sinuses originating from infection around nonabsorbable sutures. There was no apparent advantage in these cases from the use of tyrothricin insofar as the rapidity of healing was concerned. The wounds did appear cleaner, but healing did not progress until the basic difficulty was removed (e.g., the removal of suture, cauterization of overlapping skin margins, etc.).

*Bacteriology.* The method of culturing wounds was as follows:

An initial culture was inoculated at the time of operation, followed by a daily culture for the first three postoperative days, taken when dressings were changed. Subsequent cultures were usually taken at weekly intervals or when the indication arose. The predominant microorganisms found on the initial cultures were *Staphylococcus aureus* of the hemolytic and non-hemolytic varieties. Occasional cases showed beta hemolytic streptococci or a mixture of streptococci and staphylococci. Following the use of tyrothricin, there was a change in the flora of the wounds to *B. proteus* in the majority of cases within three to five days. In Group I, of the 15 cases treated with tyrothricin, 13 cases showed pure cultures of *B. proteus*. In Group II, of the eight cases in which tyrothricin was used, five cases showed *B. proteus* as the only microorganism grown. Of the 20 cases in Group III, following the use of tyrothricin, 17 cases showed *B. proteus* as the only remaining microorganism. Of the five cases in Group IV, there were two cases from which *B. proteus* was cultured following the use of tyrothricin.

These findings indicate that tyrothricin used under the conditions described above was an effective bacteriostatic substance for the microorganisms we had been accustomed to isolate from these wounds. *B. proteus* is usually a non-pathogenic microorganism and since this was the principal microorganism cultured following the use of tyrothricin, we feel that this is supporting evidence for our clinical impressions of wound healing already described.

*Summary.* The authors of this section of the present report were in charge of a pilonidal cyst ward from October 1, 1943 to September 19, 1945. During this period there were 185 admissions. These included pilonidal cysts with sinuses, recurrent pilonidal cysts, wounds from breakdown of pilonidal cyst scars and acute abscess arising in pilonidal cysts. In an effort to find a more suitable agent than those previously used to promote rapid, healthy healing of open granulating wounds, tyrothricin was employed. From our observations, the following conclusions were made:

1. Tyrothricin used locally on wounds following surgery on pilonidal cysts was superior in its effects on healing to any substance we had used previously.

2. The granulation tissue was cleaner and healthier and the rate of wound healing appeared to be more rapid.

3. Clinically, tyrothricin produced no injurious results on granulating

wounds and no untoward systemic effects were encountered in the cases studied.

4. The usual mixture of pathogenic microorganisms found to be present on wound cultures prior to use of tyrothricin was reduced in the majority of cases to the single microorganism, *B. proteus*, following the use of this substance.

5. Next to tyrothricin, the most effective substance used was penicillin.

### III. OBSERVATIONS ON THE EFFECTS OF TYROTHRIN IN MINOR SURGERY

(Captain Herbert E. Fitch, Jr., MC)

Tyrothricin has proved to be an important addition to our armamentarium in the treatment of minor surgical infections. The preparation is of outstanding value in its antibacterial effect as well as its property of stimulating healing by the formation of granulation tissue.

In the following cases to be reported, treatment was according to well established surgical principles. First, localization of fluctuation was established by the application of moist heat to the area of inflammation. Secondly, with intravenous or local block anesthesia, adequate surgical drainage was afforded. Thirdly, a culture was secured in order that the infecting organisms might be identified. Finally, the specific measures were taken to apply the drug to the affected areas.

After incision of the fluctuant area and removal of exudate with gentle debridement of necrotic tissue were accomplished, a plain gauze saturated with 1:5,000 tyrothricin solution was loosely packed in the wound. The pack was moistened with tyrothricin solution at intervals of four hours by using a bulb syringe, taking care not to dislodge the dressing. This procedure was carried out for 48 hours, at which time the pack was removed and the wound inspected. The pack was reinserted if it was deemed necessary, but usually only a small wick soaked with tyrothricin inserted between the skin edges was required. On the fourth day after operation dry dressings were usually sufficient and remained so until the patient was discharged from the hospital.

The observations and impressions gathered from the use of this agent can be summarized as follows: (1) There was a change in the character of the exudate in the first 24 hour period. This consisted of a lessening of the thick, purulent discharge with the appearance of a thin, almost colorless exudate. (2) There was a marked diminution or cessation of exudate in 72 hours. (3) There was a rapid development of healthy granulations with a clean appearance of the entire wound. (4) Epithelialization occurred early and complete healing was rapid.

Prompt diminution of the exudate was quite remarkable with this agent. The grayish-white appearance at the base of wounds resulting from incision

and debridement of carbuncles was not found. Rather, there was a clean, pink, healthy base with little or no discharge after 48 hours. The granulations were never exuberant enough to require removal by surgery or cautery. Scarring which resulted seemed to have been minimal.

*Summary of Cases.* 1. Cellulitis of the leg: 23 cases. Microorganism usually found, *Staphylococcus aureus*. Tyrothricin used for four days as a rule. Average length of stay in hospital after incision and drainage nine days.

2. Cellulitis of the hand and fingers: seven cases (two with infection of palmar space). Microorganism: *Staphylococcus aureus*. Average stay in hospital 12 days, 19 days for the palmar space infections, with minimal scarring and no contractures.

3. Carbuncles: six cases. Microorganism: *Staphylococcus aureus*. Rapid healing and minimal scarring. Hospitalization averaged 12 days.

4. Suppurative paronychia: (treated after removal of the nail) five cases. Rapid healing of the nail bed. No culture on these cases.

5. Furunculosis: two cases. Good results only on the incised furuncles. No effect noted on the unopened lesions.

#### IV. OBSERVATIONS ON THE EFFECTS OF TYROTHRICIN IN A LIMITED GROUP OF INFECTIOUS DERMATOSES

(Captain Morris Waisman, MC)

A brief experience with tyrothricin in dermatologic treatment has yielded a distinctly favorable impression of its value. Because of the small number of patients studied, statistical evaluation is precluded. It is hoped that the agent will become available at military hospitals where its efficacy in the treatment of dermatologic diseases, not ordinarily a cause for hospitalization in civilian practice, may be adequately appraised.

My clinical material was divided into two groups: (1) pustular infections, represented by two cases of severe folliculitis, and (2) eczematoid pyodermas, represented by a series of nine patients with superficial cutaneous lesions either the site of initial bacterial infection or secondarily infected. The secondarily infected eruptions usually were superimposed on preëxisting dermatophytosis of the feet. Cultures were taken in most cases.

The cases of pustular folliculitis, one of the beard and the other of the legs, from each of which a culture of hemolytic *Staphylococcus aureus* was isolated, showed no healing with application of tyrothricin wet dressings. (The deep folliculitides are notoriously refractory to therapy.) Neither did these cases respond to the use of conventional antiseptics, nor to penicillin and sulfonamides topically and systemically. Some benefit was gained by rupture of the pustules preliminary to application of the tyrothricin solution but satisfactory healing failed to take place. It was concluded that the inability of the agent to penetrate to the depth established by the infection in the hair follicles accounted at least in part for the poor result.

Excellent results were seen in six of nine cases of what I shall call "infected eczematoid dermatitis," to include both primary infection of the skin (Engman type and diffuse impetiginous eruptions) and secondarily infected dermatoses, notably dermatophytosis, dermatophytids and contact dermatitis (the latter often due to overtreatment of dermatophytosis). Culture in most cases disclosed the presence of hemolytic *Staphylococcus aureus* (coagulase and/or mannite positive), alone or in association with beta hemolytic streptococci. Most lesions were confined to the toes and feet, where they were characterized by dusky erythema and edema, often with well-defined borders, and exhibiting denudation of epithelium, excoriations, fissures, oozing, crusting and scaling, and scattered pustules of a peripheral overhanging ("dissecting") epidermal collarette. This condition commonly complicated dermatophytosis of the feet in troops stationed in Florida. The infection was an extremely indolent one, very resistant to treatment as a rule, often manifesting intolerance to the application of greases in any form, becoming excessively dried and irritated by alcoholic tinctures, prone to develop allergic sensitization to many topical medications (and possibly to its own autolytic products), and exhibiting multiple recrudescences and recurrences. As a group it constituted one of the most difficult therapeutic problems I had encountered.

The results obtained with 1:5,000 tyrothricin solution in the latter group of cases is therefore very dramatic, in that healing occurred in one-quarter to one-half of the time ordinarily expected and, what is just as remarkable, with no evidence of irritation of the skin and with good tissue repair, so that there were no recurrences observed among the healed cases.

Among the merits of tyrothricin in my experience must be listed freedom from irritation, rapidity of action, and specificity, as indicated by its success in lesions unresponsive to other potent bactericides, including the sulfonamides and penicillin. Worthy of investigation would be (1) determination of the antibacterial properties of tyrothricin incorporated in various types of bases, (2) establishment of minimal effective concentrations for economical and optimal utilization, and (3) evaluation of additive or synergistic effects obtained when tyrothricin is used concurrently with other antibacterial agents, topical or systemic.

#### GENERAL SUMMARY

1. Three types of cases have been presented which have been treated with tyrothricin locally. The cases comprise (1) rhinological infections, (2) surgical infections and (3) dermatological infections.

2. In the rhinological group, tyrothricin was used (1) in the treatment of sinus infections, (2) in the direct and prophylactic treatment of post-operative sinus wounds and sinuses and (3) in the prophylactic treatment of acute coryza to prevent or reduce the severity of the suppurative stage.

3. In the surgical group, tyrothricin was used (1) in a series of pilonidal cases and (2) in a series of minor surgical infections.

4. In the dermatological group, tyrothricin was used on a series of resistant infections.

5. The concentration of tyrothricin used in these cases was 0.2 mg. per c.c. (1:5,000), e.g., 1 c.c. of a 2 per cent alcoholic solution of tyrothricin was added to 100 c.c. distilled water.

6. In this study tyrothricin was found to be an effective antibiotic in controlling and preventing surface infection.

#### BIBLIOGRAPHY

1. SERGIEVE, P. G.: Clinical use of gramicidin S, *Lancet*, 1944, ii, 717.
2. DUBOS, R. J.: Bacteriocidal effect of an extract of a soil bacillus on gram positive cocci, *Proc. Soc. Exper. Biol. and Med.*, 1939, x1, 311-312.  
DUBOS, R. J., and HOTCHKISS, R. D.: The production of bacteriocidal substances by aerobic sporulating bacilli, *Jr. Exper. Med.*, 1941, lxxiii, 629-640.  
DUBOS, R. J., and HOTCHKISS, R. D.: Origin, nature and properties of gramicidin and tyrocidine, *Trans. and Stud. Coll. Phys. of Phila.*, 1942, x, 11-18.
3. LITTLE, R. B., DUBOS, R. J., and HOTCHKISS, R. D.: Gramicidin, novoxil and acriflavine for the treatment of the chronic form of streptococcic mastitis, *Jr. Am. Vet. Assoc.*, 1941, xcvi, 189-199.  
LITTLE, R. B., DUBOS, R. J., HOTCHKISS, R. D., BEAN, C. W., and MILLER, W. T.: The use of gramicidin and other agents for the elimination of the chronic form of bovine mastitis, *Jr. Vet. Res.*, 1941, xi, 305-312.  
SCHALM, W. W.: Treatment of bovine mastitis, *Jr. Am. Vet. Med. Assoc.*, 1941, xcix, 196.
4. CROWE, S. J., FISHER, A. M., WARD, A. T., JR., and FOLEY, M. K.: Penicillin and tyrothricin in otolaryngology, *Ann. Otol., Rhinol. and Laryng.*, 1943, lii, 541-572.
5. GOLDMAN, J. L.: Bacteriology of nose, sinuses and nasopharynx (Proceedings of Seminars on Recent Advances in Bacteriology and Immunology with Clinical Considerations, Gregory Schwartzman, M.D., Chairman), *Jr. Mt. Sinai Hosp.*, 1943, ix, 921-927.
6. GOLDMAN, J. L.: To be published.
7. JACOBSON, L. O., and DICK, G. F.: Normal and abnormal flora of the nose, *Jr. Am. Med. Assoc.*, 1941, cxvii, 2222-2225.
8. EBERT, E.: Local treatment of acute rhinitis with sulfathiazole, *Arch. Otolaryng.*, 1943, xxxviii, 324-327.
9. SCHOENBACH, E. B., ENDERS, J. F., and MUELLER, J. H.: The apparent effect of tyrothricin on *Streptococcus hemolyticus* in the rhinopharynx of carriers, *Science*, 1941, xciv, 217-218.



# CASE REPORTS

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## POLYOSTOTIC FIBROUS DYSPLASIA IN ONE OF NEGRO TWIN GIRLS \*

By GUY A. CALDWELL, M.D., *New Orleans, Louisiana*, and T. F. BRODERICK, JR., M.D., *Boston, Massachusetts*

### INTRODUCTION

INTEREST in cystic lesions of bone was greatly stimulated by the successful removal of a parathyroid adenoma by Mandl<sup>1</sup> in 1925. Since that time generalized osteitis fibrosa cystica of von Recklinghausen has been recognized as due to adenoma or hypertrophy of the parathyroid glands. However, the occurrence of other cystic bone lesions, either generalized or localized, without obvious abnormality of calcium and phosphorus metabolism, has been noted with increasing frequency and has aroused considerable speculation as to the nature of this condition or variety of conditions.

In 1937 Albright, Butler, Hampton and Smith<sup>2</sup> called attention to a syndrome characterized by (a) "A disseminated osteitis fibrosa (both hyper- and hypo-ostotic), with a distribution suggesting a relationship between the lesions and the nerve roots or to an embryologic defect in the myotomes; (b) areas of cutaneous pigmentation which have a distribution suggesting some connection between them and the bone lesions; (c) sexual and somatic precocity especially, if not exclusively, when the disease occurs in the female sex." Five cases were reported, 13 cases from the literature were reviewed and one published case was cited. Several of these had been unsuccessfully explored for parathyroid adenomata. Subsequently, there have been reported or resurrected from the literature over 50 cases which display the features of this syndrome and establish it as an entity.

In their review of the literature, Gorham and his co-workers<sup>3</sup> found that at least seven examples of the syndrome had been reported in females and five in males before Albright's paper appeared. The precocious puberty, however, was not evident in the males. Among the case designations were: "Precocious puberty and bone fragility" by Weil<sup>4</sup> in 1922; "Osteitis fibrosa cystica generalisata (osteodystrophia fibrosa)" by Priesel and Wagner<sup>5</sup> in 1932; an atypical form of "von Recklinghausen's neurofibromatosis of bones" by Snapper and Parisel<sup>6</sup> in 1933 and "Juvenile Paget's disease" by Hummel<sup>7</sup> in 1934. "Fibro-cystic osteitis with abnormal localization and evolution" was reported by Pagniez, Plichet and Fauvet<sup>8</sup> in 1938 in apparent unawareness of Albright's description of the syndrome in 1937. Since 1937 most of the cases have been reported as "Albright's syndrome" but Albright<sup>9</sup> feels that "Polyostotic fibrous dysplasia," as employed by Lichtenstein<sup>10a, 10b</sup> in 1938, is a more appropriate designation.

\* Received for publication May 9, 1946.

From the Tulane Orthopedic Service, Charity Hospital of Louisiana at New Orleans.

A negro girl, one of proved dizygotic twins, who manifested all the features of the complete form of this syndrome, has been observed over a period of 20 months. The case is presented as another example of polyostotic fibrous dysplasia which has special interest because of its occurrence in a negro and in but one of twins.

#### CASE REPORT

*History:* A nine year old negro girl was first seen at Charity Hospital in New Orleans on February 12, 1944. One day previously, in a neighboring town, she had sustained a slight fall with the result that she could not move her leg although pain was only moderate. An emergency splint was applied and transfer to New Orleans

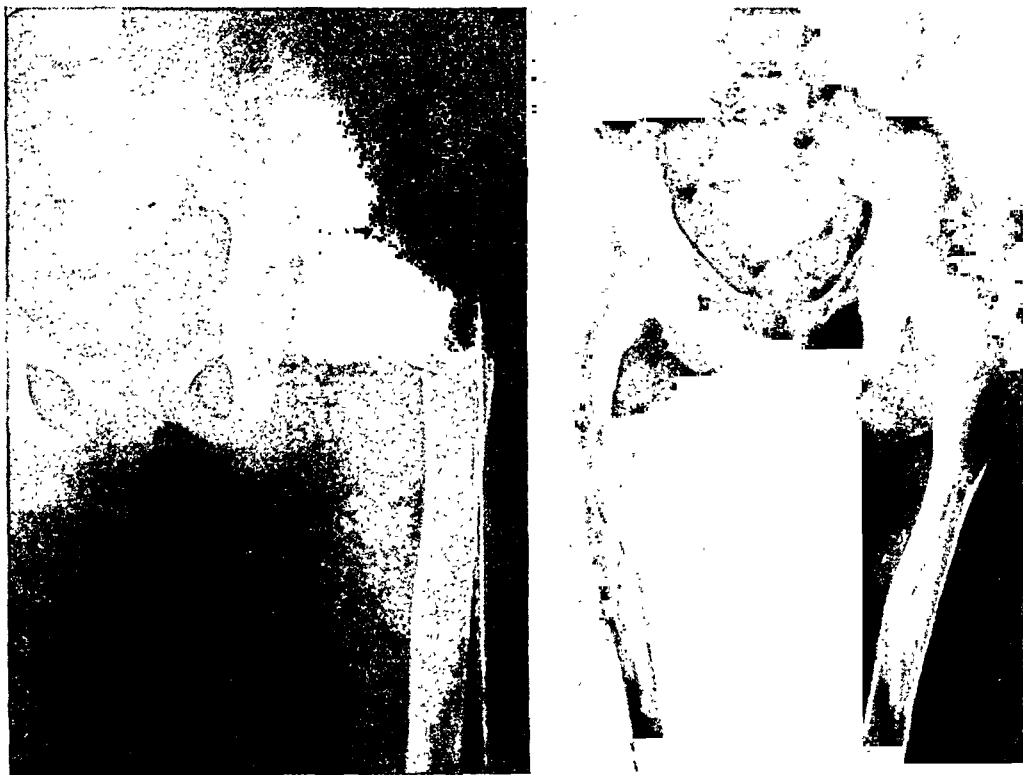


FIG. 1. (Left) February 12, 1944. Pathological fracture of left femur. Note pseudo-cystic and sclerotic areas throughout the pelvis and femur.

FIG. 2. (Right) January 10, 1945. Note healed fracture (10 months a.i.) and scattered pseudo-cystic areas, more numerous on the right side.

advised. On arrival she complained of little discomfort, although there was obvious shortening and external rotation of the left leg in the Thomas splint. Roentgenograms (figure 1) showed a subtrochanteric fracture of the left femur as well as areas of rarefaction and sclerosis throughout the pelvis and both femurs. Bilateral Russell's traction was applied.

*Physical Examination:* The patient was a tall, slender apathetic negro girl in no apparent distress who appeared to be adolescent rather than the stated age of nine years. The head was large, with increased transverse diameter of the skull and prominent frontal bosses, making the face appear relatively small and wedge-shaped. Facial movements were symmetrical but somewhat decreased in excursion. The

hair was fine, dry, brownish-black and kinky. The eyes were set wide apart, and some proptosis of the right eyeball as compared to the left was evident. The pupils reacted to light and distance. The right pupil measured 4 mm. in diameter and the left 4.5 mm. Ophthalmoscopic examination revealed atrophy of almost the entire right optic disk and of the temporal portion of the left optic disk. The vessels were normal in appearance, and neither hemorrhage nor exudation was observed. Visual coördination was poor, and visual field examination showed gross impairment for the left eye and almost complete blindness in the right eye. The nose was broad, more so than is racially normal, and the bridge was depressed. The throat, tonsils, teeth and tongue were normal. No buccal pigmentation was observed. The neck was symmetrical, and no lymph nodes were palpable. The thyroid gland could be easily palpated, but it was not obviously enlarged nor were any nodules or irregularities discernible. The thorax was noticeably asymmetrical, being more prominent on the right, and respiratory excursion was greater on that side. Breath sounds were vesicular throughout. The heart was not enlarged. Apical and pulse rates were 80 beats per minute and rhythm was regular. No murmurs were heard. Blood pressure was 118 mm. of Hg systolic and 78 diastolic. The breasts were adolescent in size and contour. The right breast and its areola were more prominent than the left breast. Axillary and pubic hair was adolescent in amount and distribution. The abdomen showed no abnormalities. The general sexual development was compatible with that of a 14 year old girl. The clitoris was enlarged to pubertal size. The hymenal ring was present but relaxed. A vaginal examination was not done. Rectal examination showed the uterus to be infantile in size and acutely anteverted. The adnexa could not be palpated. During six months of hospitalization the patient had never menstruated nor, according to the family, had menarche occurred. The extremities were grossly normal. The abdominal reflexes were present. Knee and ankle jerks were active and equal. Plantar reflexes were normal.

The skin was light brown with several patches of discoloration. Paler areas were evident over the brow and both malar bones, as though the skin were under some tension. Several black, circumscribed spots of increased pigmentation were scattered over the lower thoracic and lumbar spines, the largest of which measured 3 cm. in diameter. A saddle area of black pigmentation measuring 9 by 12 cm. extended out from the sacrum over the right buttock. No sensory changes were demonstrable in the skin of these pigmented areas.

*Course:* Bilateral Russell's traction was maintained for five weeks following which the patient was discharged in a  $1\frac{1}{2}$  spica cast. This was removed five weeks later and ambulation with crutches was permitted. The crutches were discarded after one month, and normal activity was resumed. Interval roentgenograms showed healing of the fracture but persistence of the bony lesions (figure 2).

The patient has been observed at frequent intervals over the past 20 months and additional pertinent data obtained. An attack of mumps which developed in March 1944 is worthy of note in relation to the endocrine disturbance. There have been several obvious changes in her general physical condition. Progressive enlargement of the skull with more conspicuous "wedging" of the face has been evident. Also the sexual maturity has become more apparent, but menarche has not appeared.

*Biopsy:* Biopsy material from the right ileum, left tibia and skin from the pigmented area on the right buttock was obtained on January 24, 1945. The specimens were sent to Dr. Granville A. Bennett,<sup>11</sup> Professor of Pathology at the University of Illinois College of Medicine, who made and commented on the slides which Dr. Charles E. Dunlap,<sup>12</sup> Professor of Pathology at the Tulane University School of Medicine, described as follows:

*"No. 1 Bone from right ileum (figure 3).* The major portion of the slide shows an irregular pattern of dense, closely packed, irregular trabeculae of bone. These

trabeculae are heavily calcified centrally but are bordered by a paler zone of osteoid tissue. The peripheral boundaries of the osteoid are frequently irregular and indefinite. Calcification extends from the central areas into the osteoid in a ragged fashion and the cement lines and canaliculi are not clearly defined for the most part. These changes in bone structure extend to the periosteum and no normal cortical bone remains. The marrow spaces are solidly filled with cellular fibrous tissue containing relatively little collagen. Along the margins of all the trabeculae, osteoclastic and osteoblastic activity is vigorous. At one end of the section, a chondro-osseous



FIG. 3. Photomicrograph of bone. Magnification  $\times 150$ . The trabeculae are irregular and closely packed. Each shows a central region of heavy calcification and a peripheral layer of osteoid. The marrow spaces are filled with cellular fibrous tissue.

junction is present. There is evidence of slight endochondral bone formation. Along the margin of the section farthest distant from the periosteum, the abnormalities in the bone and bone marrow terminate abruptly and give way to relatively normal bone. The marrow here is cellular and relatively normal except for the presence of many eosinophilic cells of the myelocytic series. The periosteum near the chondro-osseous junction is thicker than normal and extremely cellular, resembling the abnormal fibrous tissue present in the marrow spaces.

*"No. 2 Skin.* There is slight hyperkeratosis present particularly in numerous minor invaginations of the skin surface. The epithelial layer is thin. The basal cells contain heavy deposits of melanin. The dermal connective tissue and skin appendages are not remarkable. This section is not distinguishable from heavily pigmented normal negro skin.

"No. 3 Fragments of bone near tibial tubercle. The slide shows for the most part cortical bone of normal structure. At one point, a marrow space is filled with fibrous tissue and some reabsorption of cortical bone is apparent together with a few of the atypical trabeculae described in slide No. 1."

*Psychometric Examination:* A psychometric examination on April 13, 1945, with the revised Stanford-Binet Scale—form L, indicated that the patient was a low grade moron. Coördination and motor control were poor. She did better on verbal tests than on performance tests. The examiner felt that she displayed many stigmata associated with a feeble-minded child.

*Laboratory Studies:* Representative laboratory findings from February 1944 to October 1945 are: 3,600,000 erythrocytes per cu. mm.; hemoglobin 64 per cent; 6,400 leukocytes per cu. mm.; sedimentation rate 18 mm. per hr. (Wintrobe); urinalysis, normal; urine smears and cultures normal; no Bence Jones proteinuria; urea nitrogen 10 mg. per 100 c.c.; serum protein 6.2 gm. per 100 c.c.; icterus index 13 units; glucose 111 mg. per 100 c.c.; chlorides 685 mg. per 100 c.c. plasma; cholesterol 161–217 mg. per 100 c.c. plasma. Serologic tests for syphilis and skin tests for tuberculosis gave negative reactions.

Blood chemistry studies showed:

	<i>Calcium</i>	<i>Phosphorus</i>	<i>Alkaline Phosphatase</i>
2/15/44	10.9 mg. per 100 c.c.	5.3 mg. per 100 c.c.	26.7 Bodansky Units
2/21/44		5.0	17.2
3/13/44		4.1	19.1
5/31/44		5.25	34.7
2/ 6/45		4.8	25.4
4/19/45	12.0	4.4	26.1
6/13/45		4.5	
8/13/45	10.0	4.0	36.0

Phenolsulphonphthalein excretion was normal.

Cystoscopic examination showed a normal lower urinary tract. Roentgenograms of the kidney, ureters and bladder demonstrated kidney shadows normal in size, shape, and position. Neither calculi nor calcifications were seen. The pelves, calyces and ureters on both sides appeared to fill in a normal manner.

Satisfactory determination of the basal metabolic rate on February 20, 1945 was plus 24. Two subsequent tests gave unsatisfactory results because of poor coöperation.

*Electrocardiography:* An electrocardiogram on February 14, 1945 showed nothing more than sinus tachycardia.

*Lumbar Puncture:* Lumbar puncture on September 20, 1945 showed crystal clear fluid with a pressure of 90 to 120 mm. of water. The dynamics were normal and the Queckenstedt and Tobey-Ayer tests gave negative results. Protein, 26; glucose, 66; Pandy's test and serologic reactions were negative; cell count was 4 per cu. mm.; colloidal gold curve was normal (i.e. 1120000000).

*Roentgenography:* Complete skeletal examination has shown multiple, asymmetrically scattered areas of decreased density and sclerosis (figure 4). The skull revealed dolichocephaly (figure 5), pronounced thickening of the bones of the vault, particularly in the base with sclerosis in this region, and some few areas of decreased density within the vault. Marked sclerosis of the sphenoid bone was apparent, but the sella turcica did not appear to be enlarged. Roentgenograms of the chest were normal except for some areas of decreased density throughout the ribs. Small cystic areas were seen in most of the various bones of the extremities (figures 6 and 7). Dental roentgenograms showed calcification of the midline palate, osteoporosis of the

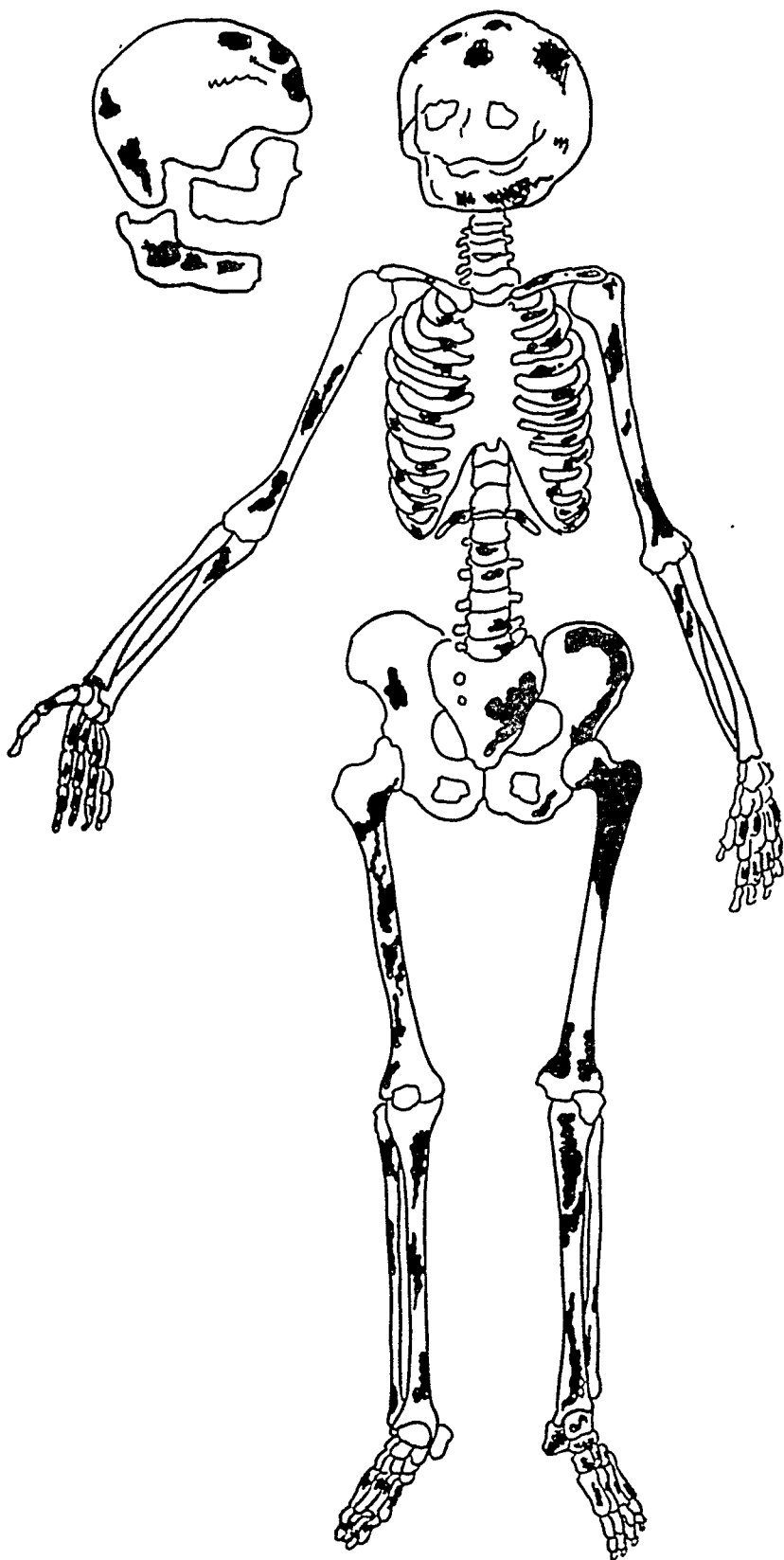


FIG. 4. Diagram showing areas of bone lesions.

mandible and maxilla and protuberance of the maxilla on both sides. Well formed second molars with eruption of the lower left second molar indicated a dental age of 13 to 14 years (figure 5). Study of various ossification centers revealed a bone age of 13 to 14 years, two to three years more than her chronologic age.



FIG. 5. Skull showing dolichocephaly, thickening of vault with a few areas of decreased density, and sclerosis of the sphenoid bone. Note presence of lower left second molar.

*Course:* In April 1945 the patient was given aluminum acetate solution orally, 1 dram three times a day after meals, supplied by Mr. A. P. Lauve, the hospital pharmacist. The preparation contained:

Solution of aluminum subacetate	545 c.c.
Glacial acetic acid	15 c.c.
	<hr/>
Water, a sufficient quantity to make	1000 c.c.

The use of aluminum acetate followed the suggestion of Helfet<sup>13</sup> that the solution possibly might reduce phosphorus intake by precipitating phosphates in the intestinal tract with resultant increase in calcium retention. Ghormley and Hinchey,<sup>14</sup> although undecided as to the physiologic action of aluminum acetate, were able to show definite roentgenographic evidence of improved calcification in a series of cases. After this patient had taken aluminum acetate for three months, her father volunteered the information that she could "see and hear better than ever before." No objective changes were evident, however, nor were there any changes in either the blood chemistry or roentgenograms.

On May 27, 1945 the patient tripped while playing and sustained a simple transverse fracture through the lower third of the left humerus (figure 8). This was reduced under general anesthesia and immobilized for eight weeks in a hanging cast. Healing was rapid, with some excess callus formation.

*Family History:* The parents were unaware of any anomalous conditions on either side of the family. The mother and father are now 43 and 39 years old respectively. There are eight children: a 15 year old daughter; the 11 year old patient and her twin sister; eight year old twin boys; a five year old son; a three year old girl and a 1½ year old baby girl. Other than the patient no one in the family has had any serious or unusual illness.

*The Twin Sister:* Studies were made to determine whether the twins were monozygotic or dizygotic since it was hoped that the differentiation might clarify the nature of this obscure condition. However, examination of several traits which

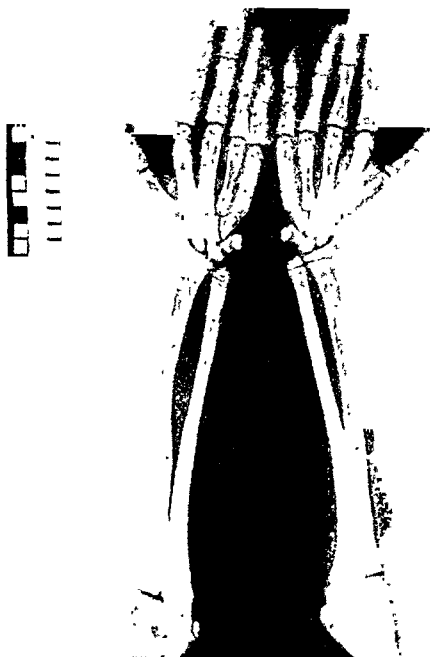


FIG. 6. (Left) January 10, 1945. Forearms and hands showing asymmetrical pseudo-cystic areas. Note absence of involvement of several small bones.

FIG. 7. (Right) January 10, 1945. Feet showing cystic changes which are slightly more extensive in right foot.

are non-linked in inheritance gave acceptable evidence that the twins are dizygotic. Although they both are blood type A, they differ in iris pigmentation, intelligence quotient, stature and quantitative value of finger prints. The finger prints were examined by Dr. Harold Cummins,<sup>15</sup> Professor of Microscopic Anatomy at Tulane Medical School, who concluded that the twins were dizygotic and also that there were no aberrant features in the patient's handprints to suggest a systemic disease.

The twin sister is a normal child and the parents reported a progressive disparity in the two children from about the age of three years (figures 9, 10, and 11). The normal twin developed more rapidly, walked and talked almost one year earlier than the patient, and made average progress in school. The patient never progressed beyond the first grade. Comparative measurements taken in April 1945 were:

	Patient	Normal Twin
Height	130 cm.	135 cm.
Weight	63 lb.	61 lb.
Crown	59 cm.	53 cm.



Physical examinations of the normal twin have disclosed no abnormalities. Roentgenographic examination of her entire skeleton in March 1944 gave negative findings except for spina bifida occulta of the fifth lumbar vertebra. The bone age was compatible with her chronologic age. Electroencephalogram for the twin made in October 1945 was interpreted as that of a normal 10 year old child whereas that of the patient resembled more nearly the record of a 40 year old woman. Dental examination showed that the twins have the same number of caries in the same position in the



FIG. 8. May 29, 1944. Pathological fracture of right humerus. Note cystic areas, expansion of mid-shaft and thinning of cortex.

same teeth. However, the patient's caries were definitely more advanced and this may have some relationship to her more mature degree of calcification.

Routine blood studies on the twin yielded findings within normal limits. Her blood chemistry showed:

	<i>Calcium</i>	<i>Phosphorus</i>	<i>Alkaline phosphatase</i>
3/28/44	—	5.0 mg./100 c.c.	6.4 Bodansky Units
4/19/45	12.4 mg./100 c.c.	4.5	7.5

A five year old niece (L-44-16104B) of the twins was admitted to Charity Hospital in January 1945 with complaints of vertigo, nystagmus and weakness. Medical investigation was non-contributory, and the patient was discharged with a diagnosis of possible brain tumor. Certain familial resemblances to our patient were noted, and it was suggested that her symptoms might be attributed to an allied con-

dition. However, physical examination, skeletal roentgenograms and blood chemical determinations for calcium, phosphorus and alkaline phosphatase were within normal limits. No additional data have yet been collected on this patient.

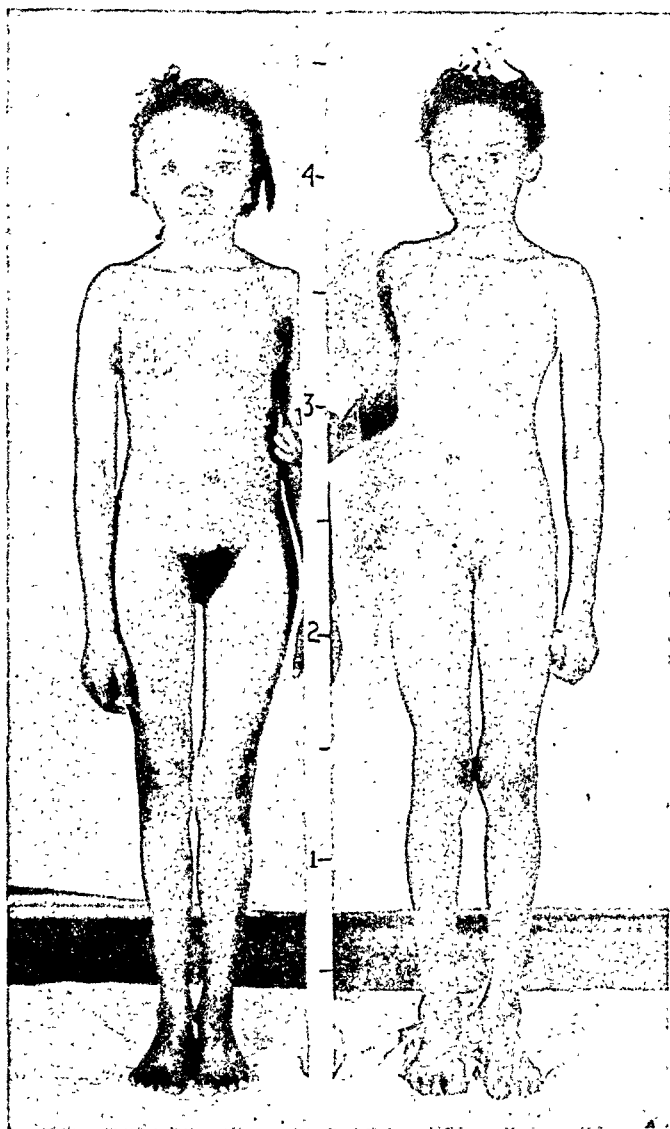


FIG. 9. April 19, 1945. Patient. Normal twin sister. Note deformity of skull, mammary development, pubic hair and body contour as compared to twin.

#### ETIOLOGY

Albright and his associates<sup>2</sup> originally suggested a neurologic or embryonic defect as the etiologic factor since the peculiar distribution of osseous and cutaneous lesions would tend to exclude primary metabolic or endocrine factors. Evidence is accumulating which supports this embryonic interpretation. Albright, Scoville and Sulkowitch<sup>10</sup> in 1938 described the occurrence of the syndrome in a 21 year old man who showed neurologic changes in reflexes and in sensation in relation to the pigmented skin lesions. They also cited the work of

Ford and Guild,<sup>17</sup> who observed sexual precocity following injuries, infections and pineal tumors involving the region of the hypothalamus.

Freedman<sup>18</sup> described the clinical features of this syndrome in 1932 under the title of "Disturbance of the Function of the Suprarenal Glands." This patient was later included as case No. 3 in Albright's paper in 1937 and subse-

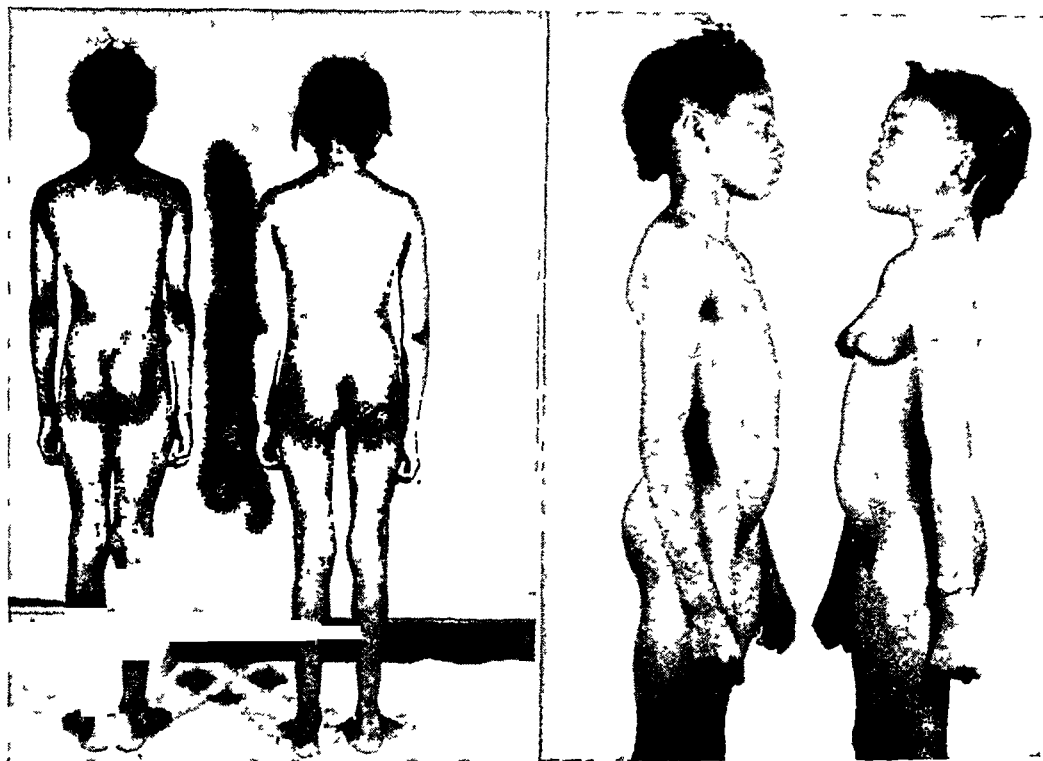


FIG. 10. (Left) Same. Note broad hips of patient and pigmented areas over spinal column and in gluteal region.

FIG. 11. (Right) Same.

quently came to autopsy. Dr. H. E. MacMahon,<sup>19</sup> Professor of Pathology at Tufts College Medical School, who studied the postmortem material, kindly wrote us concerning his findings. In respect to the central nervous system he noted "many anomalies of the brain and included among these was an alteration involving the hypothalamic nuclei along one side. It gave the appearance of an accessory nucleus with well formed nerve cells and axones, though it could equally well have been an asymmetrical division of one of the ganglia in which one portion appearing as an accessory nucleus lay in very close apposition to one of the nuclei normally found." Dr. MacMahon expects to report this case soon.

### DISCUSSION

The most striking features of the case reported are the obvious endocrine dysfunction, the generalized but asymmetrical skeletal involvement, the premature physical development and epiphyseal closure, and the patchy skin pigmentation which has little apparent relation to the skeletal lesions. There is no evidence to support the assumption that heredity, environment or infection are

etiologic factors. Albright's hypothesis that this is a neurologic defect in the region of the hypothalamus on an embryonic basis seemingly is the most logical starting point for any attempt to explain and correlate our observations.

Continued study of this case may reveal many valuable clues concerning the nature and course of this unusual condition. Of particular interest are:

1. A check on the urinary excretory rates of pituitary gonadotropins, estrogens and 17-ketosteroids to see if they are proportionate to the degree of maturation rather than to the chronologic age.
2. Will progesterin induce menstruation, that is, is the follicle-stimulating hormone secreted by the anterior pituitary but not the luteinizing hormone?
3. Will the condition become stationary after epiphyseal union?
4. Will malignant degeneration occur? Coley and Stewart<sup>20</sup> recently reported bone sarcoma developing in two cases of polyostotic fibrous dysplasia. They described essentially identical histologic patterns of pleomorphic spindle and giant cell sarcomata for both cases. Each case showed evidence of metastasis and also had an unusual response to radiotherapy.
5. What will be the effect and action of aluminum acetate on the bone lesions?

#### SUMMARY

A patient with polyostotic fibrous dysplasia examined over a period of 20 months has shown some clinical maturation but little physiologic change in that period. This case is unusual because the patient was a negro and had a normal dizygotic twin. Diagnosis is based on widespread but asymmetrical fibrous dysplasia of the skeleton, precocious puberty, patchy pigmentation of the skin, and repeatedly normal values of blood calcium and phosphorus although alkaline phosphatase was consistently elevated. A primary germ plasm defect is the most plausible etiologic hypothesis. Continued study of this case may contribute to our knowledge of this unusual entity.

*Note:* The authors wish to express their sincere appreciation to Granville A. Bennett, M.D., Professor of Pathology at the University of Illinois College of Medicine, for stimulating interest in this case and for preparing and examining the biopsied material; to Charles E. Dunlap, M.D., Professor of Pathology at Tulane University Medical School; Fuller Albright, M. D., Assistant Professor of Medicine, Harvard Medical School; H. E. MacMahon, M.D., Professor of Pathology and Bacteriology, Tufts College Medical School; Harold Cummins, Ph.D., Professor of Microscopic Anatomy, Tulane University Medical School; Josephine E. Ferguson, Medical Social Service Department, Charity Hospital, and to the various services at Charity Hospital for their aid and constructive criticisms. The photomicrograph was made by Dr. Dunlap. Miss Vera Morel and Mr. Meade of the Art Department at Tulane University Medical School supplied the diagram and the photographs respectively.

#### BIBLIOGRAPHY

1. MANDL, F.: *Therapeutischer Versuch bei Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors*, Wien. klin. Wchnschr., 1925, xxxviii, 1343.
2. ALBRIGHT, F., BUTLER, A. M., HAMPTON, A. O., and SMITH, P.: *Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females; report of 5 cases*, New England Jr. Med., 1937, ccxvi, 727-746.

3. GORHAM, L. W., and others: Albright's syndrome; group of cases characterized by osteitis fibrosa disseminata, areas of pigmentation and gonadal dysfunction, *Clinics*, 1942, i, 358-385.
4. WEIL: Pubertas praecox und Knochenbrüchigkeit, *Klin. Wchnschr.*, 1922, i, 2114.
5. PRIESEL, R., and WAGNER, R.: Ostitis fibrosa cystica generalisata (*Osteodystrophia fibrosa*), *Ztschr. f. Kinderh.*, 1932, liii, 146-161.
6. SNAPPER, L., and PARISEL, C.: Generalized xanthomatosis of bones (confusion with Recklinghausen's disease), *Maandschr. v. kindergeneesk.*, 1933, ii, 359-377.
7. HUMMEL, R.: Zwei Fälle von Ostitis deformans Paget juvenilis, *Röntgenpraxis*, 1934, vi, 513-519.
8. PAGNIEZ, P., PLICHET, A., and FAUVET, J.: Un cas d'ostéite fibro-kystique de localisation et d'évolution anormales, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1938, liv, 733-736.
9. ALBRIGHT, F.: Personal communication.
- 10a. LICHTENSTEIN, L.: Polyostotic fibrous dysplasia, *Arch. Surg.*, 1938, xxxvi, 874-878.
- 10b. LICHTENSTEIN, L., and JAFFE, H. L.: Fibrous dysplasia of bone, *Arch. Path.*, 1942, xxxiii, 777-816.
11. BENNETT, G. A.: Personal communication.
12. DUNLAP, C. E.: Personal communication.
13. HELFET, A. J.: New concepts of parathyroid function and its clinical application; preliminary report on results of treatment of generalized fibrocystic and allied bone diseases and of rheumatoid arthritis by aluminum acetate, *Brit. Jr. Surg.*, 1940, xxvii, 651-677.
14. GHORMLEY, R. K., and HINCHEY, J. J.: Use of aluminum acetate in the treatment of malacic diseases of bone, *Jr. Bone and Joint Surg.*, 1944, xxvi, 811-817.
15. CUMMINS, H.: Personal communication.
16. ALBRIGHT, F., SCOVILLE, W. B., and SULKOWITCH, H. W.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and gonadal dysfunction; further observations including report of 2 more cases, *Endocrinology*, 1938, xxii, 411-421.
17. FORD, F. R., and GUILD, H.: Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with discussion of relation of intracranial tumors and inflammatory processes to syndrome of macrogenitosomia praecox, *Bull. Johns Hopkins Hosp.*, 1937, lx, 192-203.
18. FREDMAN, H. J.: Disturbances of function of suprarenal glands in children, *Am. Jr. Dis. Child.*, 1932, xlv, 1285-1292.
19. MACMAHON, H. E.: Personal communication.
20. COLEY, B. L., and STEWART, F. W.: Bone sarcoma in polyostotic fibrous dysplasia, *Ann. Surg.*, 1945, cxxi, 872-881.

## HEART TRAUMA: MYOCARDIAL INVOLVEMENT (CONTU- SION) FOLLOWING A NON-PENETRATING INJURY TO THE CHEST (AIRPLANE ACCIDENT) \*

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A NUMBER of recent reviews have pointed to the apparent frequency with which non-penetrating injuries to the chest are complicated by lesions of the heart.<sup>1-6</sup> In most of the earlier reports the injury to the heart was striking, im-

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From the Department of Medicine, University of Utah Medical School, Salt Lake City, Utah. The case was observed on the wards of the Wm. J. Seymour Hospital, Eloise, Michigan.

mediate, and either fatal or incapacitating. In others severe cardiac failure, conduction disturbances or rupture of the myocardium occurred after a relatively silent period.† The subject has become increasingly important from the standpoint of industrial<sup>5, 8, 9, 10, 11</sup> and military<sup>3, 4, 12-15</sup> compensation. The use of early and repeated electrocardiographic examinations has been stressed as being necessary in the presence of any injury to the chest, as it has become apparent that cardiac involvement may occur with little or no other evidence to indicate its existence. However, very few attempts have been made to interpret the electrocardiographic findings obtained or to recognize in reporting the electrocardiographic abnormalities in cases of this type that extensive aberrations of a presumably "normal" pattern may occur in otherwise healthy individuals.<sup>16, 17</sup>

The following example is described because it represents a type of injury hitherto not reported as a cause of traumatic heart disease. It is likely, however, that proper examination will reveal a high incidence of myocardial involvement in accidents of this type.

Furthermore, the example illustrates that careful clinical observation with frequent electrocardiograms including a number of precordial leads may reveal temporary involvement of the heart muscle which would be easily missed on a routine accident service.

#### CASE REPORT

The accident involved a 34 year old American civilian air pilot and engine instructor who had always been in excellent health and had successfully passed an army examination for air cadet rating three weeks before. On June 6, 1943, during a routine flight in a three seater open cockpit plane the engine stalled at 400 feet. He crash-landed in a marshy clearing, the plane nosed over and the patient was violently yanked forward into his safety-belt. When admitted to the hospital two hours later he was found to be in shock with evidence of severe crushing injuries to the left lower chest, left upper abdomen and to the back. Roentgenograms revealed fractures of the left fifth and sixth ribs and of the right sixth and tenth ribs. There was a fracture of the sacrum with extension into the iliac crest, a fracture of the transverse processes of the fifth lumbar vertebra and comminuted fractures of the right radius and ulna and of the left tibia and fibula. There was a small collection of fluid in both pleural cavities. The patient responded well to treatment and received a total of 500 ml of plasma, 500 ml of whole blood and 2000 ml of 5 per cent glucose in saline solution during the first 24 hours. A complete physical examination performed on the morning of the first hospital day was normal except for a few scattered râles in both lung fields and the injuries noted above. The blood pressure had risen from the admitting level of 90 mm. of mercury systolic and 60 diastolic to 110 systolic and 70 diastolic. The heart sounds were forceful and of equal intensity over the base, and no enlargement and no murmurs were noted. The rhythm was regular but rapid (130 beats per minute). On the evening of the first day (24 hours after the injury) the patient received 10 ml of adrenal cortical extract intramuscularly. Two hours later the patient was found to be in acute distress; he was intensely cyanotic, severely dyspneic and perspired profusely. The heart sounds appeared muffled and the pulse rate had risen to 145 beats per minute. The lungs

† Joachim and Mays<sup>7</sup> noted a ventricular aneurysm 12 years after a chest injury in a 24 year old man. A similar instance was reported by Hildebrandt (E. Warburg I.c.), in which a ventricular aneurysm was present in a 27 year old individual 18 years after injury. No other cause for the aneurysm was found in either case. Compensation was granted to a man who suffered incapacitating attacks of the Adams-Stokes variety with complete a.v.-block beginning nine months after a chest injury.<sup>8</sup>

were not examined at this time. The patient was immediately given oxygen and received 0.5 gm. aminophyllin and 2 ml salyrgan intravenously. Within the next hour he began to improve and by midnight had all but completely recovered from this episode. A lumbar puncture during this time revealed normal findings. When seen the following morning by a medical consultant the patient appeared comfortable and was breathing normally. The heart was found to be slightly enlarged although the patient's stocky build made a proper evaluation of the heart size difficult. A per-

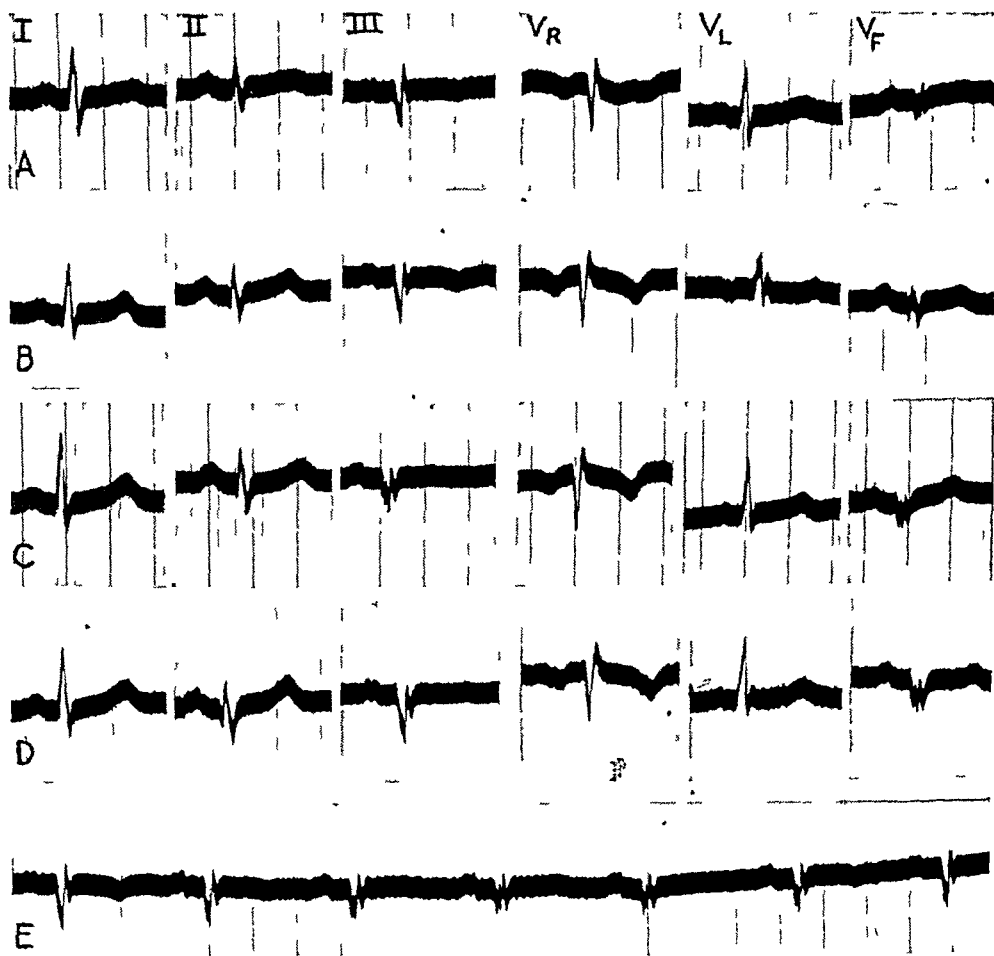


FIG. 1. Standard limb leads and unipolar limb leads (extremity potentials) of right arm ( $V_R$ ), left arm ( $V_L$ ) and left leg ( $V_F$ ). (A) 6.14, (B) 6.18, (C) 6.23, (D) 12.4.1943, (E) 6.18.1943: Lead III during forced respiration. No striking changes were noted in any of the leads illustrated or in others taken during the same period.

sistent tachycardia (130 per minute) in the face of a now almost normal temperature was noted and a diastolic gallop rhythm was distinctly audible over the apex. There were no râles in the chest. No specific therapy was instituted, but from the findings an injury to the heart muscle was suspected. This appeared even more likely from the fact that the gallop rhythm persisted until the fifth hospital day and that the pulse rate remained elevated (above 100 beats per minute) until the eleventh hospital day. The patient made a gradual and uneventful recovery. He was discharged 20 days after his accident, and when seen six months later was quite well except for a non-union of the left wrist following the fracture.

The first electrocardiogram was taken on the fourth hospital day (June 11, 1943). The three standard limb leads recorded at this time were similar in all respects to those recorded at later dates (figure 1). They always revealed left axis deviation of QRS and of T with definite Q waves in Lead III. The configuration of QRS was observed to change considerably during respiration (figure 1 E).

The tracings mounted on the right hand side of figure 1 are the so-called unipolar limb leads (extremity potentials). In recording these one of the electrodes is placed in rotation on the right arm ( $V_R$ ), left arm ( $V_L$ ), or the left leg ( $V_F$ ). The other electrode is connected to a neutral or ground connection, the central terminal. It

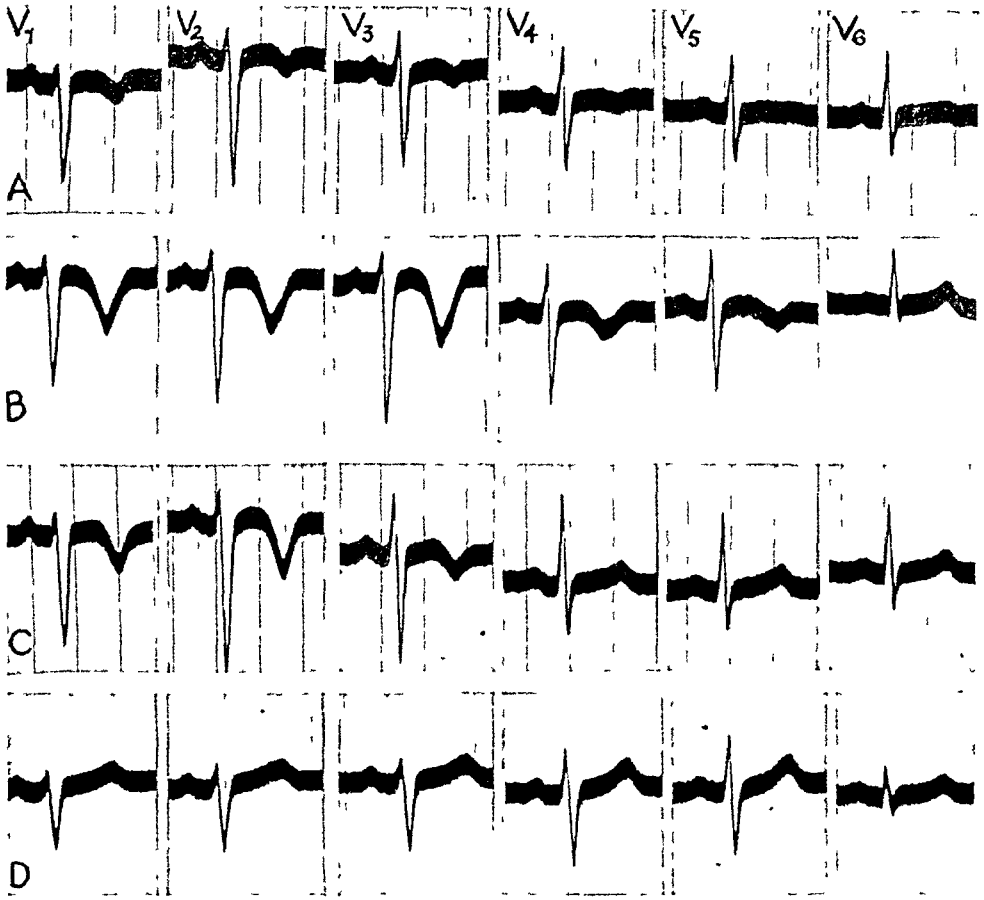


FIG. 2. Serial precordial leads:  $V_1$  at fourth intercostal space, right sternal border,  $V_2$  at fourth intercostal space left sternal border,  $V_3$  half way between  $V_2$  and  $V_4$ ,  $V_4$  at fifth intercostal space left midclavicular line,  $V_5$  on horizontal level with Lead  $V_4$  but in anterior axillary line,  $V_6$  as  $V_5$  but in left midaxillary line. (A) to (D) as in figure 1.

has been shown that the central terminal is practically void of variations in electrical potentials during the cardiac cycle<sup>18</sup> and consequently by using such an arrangement a record is obtained which represents the potential variations under one electrode only, in this case under the electrode placed in rotation on the extremities. Standard limb leads are records representing the summation of the variations in electrical potentials of two extremities and consequently each unipolar limb lead represents one half of a standard lead. With minor variations these unipolar limb leads had changed but little: the right arm lead ( $V_R$ ) showed inversion of all electrocardiographic components, which is the rule in a normally activated heart. The left arm ( $V_L$ )



revealed large R waves at all times and the left leg ( $V_F$ ) invariably showed small primary downward directed QRS complexes. This pattern is indicative of a horizontally placed heart.<sup>19</sup> Standard Lead III is expressed as the sum of the potentials of the left leg minus those of the left arm ( $V_F - V_L$ ). This means that the large R waves present in  $V_L$  must be subtracted from the potentials of  $V_F$ . This will result in either deep Q waves or deep S waves in Lead III. The presence of deep Q waves in Lead III in the tracing obtained must therefore be considered as a result of the horizontal position of the patient's heart within the chest and cannot be considered an abnormal finding. Esophageal leads were taken on one occasion and revealed a normal pattern. The fact that the complexes in Lead III could be altered considerably during deep inspiration when the heart was being rotated around its longitudinal axis (figure 1 E) constitutes further proof for the normality of the pattern present. These findings are stressed because Q waves of the type recorded are invariably observed in instances of posterior myocardial infarction. This diagnosis could be excluded on many grounds.

In contrast to the essentially normal electrocardiographic findings in standard leads and in unipolar limb leads (figure 1), striking changes were recorded in the usual six precordial leads (figure 2). The first series (figure 2 A) was taken on June 14, 1943—seven days after the accident—and revealed flat T waves over the left ventricle ( $V_4, V_5, V_6$ ) and a terminal inversion of the T waves in leads from the right side ( $V_1 - V_3$ ). Four days later the inversion of T had extended to include all but one lateral chest lead ( $V_6$ ) and the T wave inversion had now become very pronounced in the first three leads (figure 2 B). Still later, on June 23, 1945—16 days after the accident—T waves had returned to normal over the left ventricle but still showed sharp inversion in Leads  $V_1, V_2$  and  $V_3$  (figure 2 D). Tracings taken six months later revealed an essentially normal pattern in all leads (figure 2 E). At no time during the episode were changes observed involving the QRS complex or the RST junction.

## DISCUSSION

The case presented is of interest because: (1) a nonpenetrating trauma was capable of causing apparently substantial though transient myocardial injury; (2) myocardial involvement was not readily apparent before the third hospital day, and the peak of the electrocardiographic abnormalities occurred during the second week following the accident; (3) the electrocardiographic changes were confined to the final portion of the T wave; and (4) the electrocardiographic alterations were confined to certain precordial leads only.

Injuries to the heart muscle have been produced experimentally by direct blows to the heart muscle<sup>20</sup> or to the chest wall<sup>22, 23</sup> and in man apparently result from simple transmission of the traumatic force in a resilient and flexible thoracic cage.<sup>1, 4, 12</sup> Barring immediate rupture of the heart with sudden death, the myocardium may be involved in one of three ways. First, an endocardial tear may penetrate into the myocardium. In instances of this type partial rupture of the myocardium may become complete and sudden death may occur following a latent interval.<sup>1, 3, 6, 7, 10</sup> In other cases the injury may result in bruises to the myocardium consisting of extravasation of blood into the myocardium with rupture of myocardial fibers, secondary leukocytic infiltration, edema, resolution and finally scar tissue formation.<sup>1, 13, 19-25</sup> Such lesions usually spread from the epicardial surface inward. Hemopericardium, myocardial scarring with aneurysm of the type mentioned above or even rupture may result<sup>26</sup> although complete functional recovery with dense scar formation appears to be

more common. The third type consists of direct injury to the coronary arteries and results in secondary myocardial infarction. True examples of this type are not common, and many reports of "traumatic" coronary occlusion such as those reported by Leinoff, Lee and Boas<sup>9, 14, 27</sup> may be re-interpreted as instances of contusion or primary scarring of the heart muscle. That intimal hemorrhage into a previously atheromatous coronary artery may follow external violence and result in the typical clinical syndrome appears logical, however, and is attested to in a number of reports<sup>3b, 4, 9a, 27-32</sup> though repeatedly challenged by Master and his associates.<sup>33</sup> Even an apparently normal coronary system may be damaged to an extent resulting in occlusive thrombus formation.<sup>34</sup>

In the present case the injury was severe enough to cause an episode of left ventricular failure with a paroxysm of dyspnea 24 hours after the injury and to produce a persistent gallop rhythm during the first week. That this was apparently the result of a myocardial contusion involving epicardial layers but not penetrating deeply can be clearly argued from the characteristic electrocardiograms obtained. The latent period before the inversion of T makes its appearance has been observed by others. This delay is comparable to that of the T wave inversion associated with myocardial infarction secondary to coronary occlusion. Here T wave changes also occur late, in contrast to the almost immediate changes of QRS and of the RST-junction, and they appear most pronounced at a time when regenerative processes in the infarcted area are at their height. Injuries of the kind discussed are grossly and histologically similar to those produced by acute occlusion of a coronary artery<sup>13, 20, 34, 25</sup> with the exception that the latter usually involves a greater area and as a rule traverses almost the entire thickness of cardiac muscle. This penetrance of myocardial infarctions accounts for the frequency with which alterations of the QRS complexes are encountered. Deeply penetrating myocardial infarcts cause a decrease in R and the appearance of deep Q waves due to the escape of primarily negative potentials of the ventricular cavities through the electrically inert infarcted muscular wall to the surface and thence to the periphery.<sup>35</sup> In the case presented enough healthy and active muscle must have been present underneath the lesion to prevent such changes from occurring. Infarcts imbedded in layers of relatively normal muscle tissue are occasionally observed presenting only T wave changes.<sup>19</sup> A limited destruction of this type closely resembles the hemorrhagic areas experimentally produced or actually encountered in myocardial contusions.<sup>1, 6, 13, 20-25</sup> The absence of changes of QRS complex in this case and in those reported by others is then compatible with the superficiality of the lesion. This could be either endocardial or epicardial. An endocardial tear would be expected to result in QRS changes of the vibratory type and in little if any alteration of T. The characteristic pattern of subendocardial necrosis as described by others<sup>36</sup> was absent. It appears from experimental studies and from autopsy examinations that the typical myocardial contusion involves the epicardial muscle layers and in that respect can be compared with the changes of the heart muscle associated with pericarditis. One might effectively argue that many of the electrocardiographic findings on record and those reported in the case presented were of the type suggesting pericarditis. Pericardial involvement is indeed common in non-penetrating chest injuries.<sup>37</sup> In Warburg's series<sup>3</sup> pericarditis was clinically suspected in 30 and was found in 15 of 60 cases which came to autopsy (25 per

cent). The electrocardiographic changes in direct lacerating wounds of the heart are likewise often dominated by those ascribable to an accompanying pericarditis.<sup>38-40</sup> As the electrocardiographic changes of pericarditis are due to involvement of superficial myocardial layers,<sup>41</sup> the differentiation between electrocardiographic changes of "traumatic" pericarditis and those produced by direct bruising of the myocardium becomes immaterial. The tracing which was recorded was one which presented the typical picture of lesions of the epicardial muscle layers. The use of multiple precordial leads gives further clues as to the exact location of the epicardial injury. Chest leads  $V_1$ ,  $V_2$  and  $V_3$ —leads close to the sternum—were primarily affected, suggesting that the lesion faced straight anteriorly, involving the surface of the right and left ventricles but not involving the apical region. Such an "antero-septal" location is not deflected to the extremities<sup>19</sup> and consequently escapes detection by the conventional methods.

Not only the location but also the degree of involvement can be estimated from the electrocardiographic pattern. No striking upward displacement of the RST junction was observed. If present, it is associated with acute severe injury to the heart muscle. It is unlikely that RST displacement was present but escaped detection, because the gradual waxing and waning of the changes seen in figure 2 permits the assumption that alterations of the ventricular complexes began at or very shortly before the time the first tracing was recorded. T wave changes of the kind presented and without striking elevation of the RST-junction are seen at marginal regions of experimental infarctions where collateral circulation is active and where the injury set by the arterial occlusion is least pronounced.<sup>36</sup> It appears from recent observations that T wave inversion may precede ST displacement as an early sign in the event of progressive myocardial ischemia.<sup>42</sup> It has been shown that terminal T wave inversion was the first change to occur when a coronary artery of a dog was clamped for a short period of time. A more prolonged clamping caused ST displacement and finally QRS changes of the classical pattern were produced. The absence of RST displacement in the records obtained from this patient must indicate a relatively mild injury, an assumption which is well supported by the gradual disappearance of all clinical and electrocardiographic signs.

In conclusion the injury observed must have been mild and superficial. It involved the epicardial layers of heart muscle of the anterior surface and did not extend to the apical region. The changes were not evident in any of the standard limb leads and extremity potentials. A routine chest lead (IVF) would have given little additional information. The gradual appearance, extension and involution of the lesion seen in precordial leads fulfilled the prophecy of White and Glendy that "the electrocardiogram will become a very important aid in the estimation of the amount of damage both structural and functional which the heart muscle suffers as the result of the injury."<sup>43</sup>

#### SUMMARY

1. A severe nonpenetrating injury to the chest resulted in transient myocardial injury as evidenced by:

- a. Onset of left ventricular failure 24 hours after injury.
- b. Persistent tachycardia and gallop rhythm during the first week following the injury.
- c. Progressive electrocardiographic changes from the first to the third week after the accident.

2. The resulting lesion was judged to be superficial because of the absence of demonstrable ST displacement. It was thought to be epicardial because the electrocardiographic pattern obtained was similar in many respects to the changes observed in certain stages of pericarditis.

3. The location of the lesion made its detection possible only by the use of multiple precordial leads. These, in addition, allowed some insight into the progression, extension and involution of the process.

#### BIBLIOGRAPHY

1. BRIGHT, E. F., and BECK, C. S.: Non-penetrating wounds of the heart, *Am. Heart Jr.*, 1935, x, 293.
2. BARBER, H.: Trauma of the heart, *Brit. Med. Jr.*, 1938, i, 433.
- 3a. WARBURG, E.: Subacute and chronic pericardial and myocardial lesions due to non-penetrating traumatic injuries, 1938, Oxford University Press, London.
- b. WARBURG, E.: Myocardial and pericardial lesions due to non-penetrating injury, *Brit. Heart Jr.*, 1940, ii, 271.
- 4a. SIGLER, L. H.: Trauma of the heart due to nonpenetrating chest injuries, *Jr. Am. Med. Assoc.*, 1942, cxix, 855.
- b. SIGLER, L. H.: Traumatic injury of the heart, *Am. Heart Jr.*, 1945, xxx, 459.
5. AHRENBURG, H.: Traumatic heart disease: a clinical study of 250 cases of nonpenetrating chest injuries and their relation to cardiac disability, *Ann. Int. Med.*, 1943, xix, 326.
6. BARBER, H.: The effects of trauma, direct and indirect, on the heart, *Quart. Jr. Med.*, 1944, xiii, 137.
7. JOACHIM, H., and MAYS, A. T.: A case of cardiac aneurysm probably of traumatic origin, *Am. Heart Jr.*, 1926-27, ii, 682.
8. KESSLER, H. H.: Accidental injuries, 2nd ed., 1941, Lea and Febiger, Philadelphia.
- 9a. LEINOFF, H. D.: Direct nonpenetrating injuries of the heart, *Ann. Int. Med.*, 1940, xiv, 653.
- b. LEINOFF, H. D.: Acute coronary thrombosis in industry, *Arch. Int. Med.*, 1942, lxx, 33.
10. FOSTER, R. F.: The relation of trauma to heart disease, *Indust. Med.*, 1938, vii, 258.
11. ANDERSON, R. G.: Nonpenetrating injuries of the heart, *Brit. Med. Jr.*, 1940, ii, 307.
12. FORESEE, J. A., SHEFTS, L. M., BURBANK, B., FITZPATRICK, L. J., and BURFORD, TH. H.: The management of thoracic war injuries, *Jr. Lab. and Clin. Med.*, 1943, xxviii, 418.
13. WILSON, J. V.: The pathology of closed injuries of the chest, *Brit. Med. Jr.*, 1943, i, 470.
14. LEE, R. V., USSHER, N. T., and HOUGH, G. H.: Acute traumatic heart disease, *Am. Jr. Med. Sci.*, 1943, ccvi, 722.
15. LEAVELL, B. S.: Acute heart failure following blast injuries, *War Med.*, 1945, vii, 162.
16. HARTWELL, A. S., BURRETT, J. B., GRAYBIEL, A., and WHITE, P. D.: The effects of exercise and of four commonly used drugs on the normal human electrocardiogram, with particular reference to T wave changes, *Jr. Clin. Invest.*, 1942, xxi, 409.
17. WHITE, P. D., CHAMBERLAIN, F. L., and GRAYBIEL, A.: Inversion of the T waves in Lead II caused by a variation in the position of the heart, *Brit. Heart Jr.*, 1941, iii, 233.
18. WILSON, F. N., JOHNSTON, F. D., MACLEOD, A. G., and BARKER, P. S.: Electrocardiograms that represent the potential variations of a single electrode, *Am. Heart Jr.*, 1934, ix, 447.
19. WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F., ERLANGER, H., KOSSMANN, C. E., HECHT, H., COTRIM, N., MENEZES DE OLIVEIRA, R., SCARSI, R., and BARKER, P. S.: The precordial electrocardiogram, *Am. Heart Jr.*, 1944, xxvii, 19.
20. MORITZ, A. R., and ATKINS, J. P.: Cardiac contusion, *Arch. Path.*, 1938, xxv, 445.
21. BOYD, L. J., and SCHERF, D.: El electrocardiograma en las injurias epicárdicas, endocárdicas (y miocárdicas subyacentes) localizadas, *Rev. argent. de cardiol.*, 1940, vii, 1.
22. SCHLOMKA, G.: Commotio cordis und ihre Folgen, *Ergebn. d. inn. Med. u. Kinderh.*, 1934, xlvii, 1.

23. KISSANE, R. W., FIDLER, R. S., and KOONS, R. A.: Electrocardiographic changes following external chest injuries to dogs, *Ann. Int. Med.*, 1937, xi, 907.
24. SCHERF, D., and TERRANOVA, R.: Estudio electrocardiográfico de las desviaciones del segmento ST en las contusiones torácicas experimentales, *Rev. argent. de cardiol.*, 1942, ix, 157.
25. FORERO, A., SILVA, B., and SAFFIE, F.: Estudio electrocardiografico y anatomico del traumatismo precordial experimental, *Rev. argent. de cardiol.*, 1944, xi, 77.
26. KRUMBHAR, E. B., and CROWELL, C.: Spontaneous rupture of the heart, *Am. Jr. Med. Sci.*, 1925 clxx, 828.
27. BOAS, E. P.: Angina pectoris and cardiac infarction from trauma or unusual effort, *Jr. Am. Med. Assoc.*, 1939, cxii, 1887.
28. SCHMINCKE, A.: Beitrag zur traumatischen Aetiologie der Arteriosklerose, *Deutsch. Arch. f. klin. Med.*, 1925, cxlix, 145.
29. KIENLE, F.: Klinische und elektrokardiographische Beobachtungen bei traumatischem Hinterwand Infarkt, *Ztschr. f. Kreislaufforsch.*, 1938, xxx, 674.
30. BOAS, E. P.: Some immediate causes of cardiac infarction, *Am. Heart Jr.*, 1942, xxiii, 1.
31. JEKL, E., and GREENSTEIN, J.: Fatal coronary sclerosis in a boy of 10 years, *Lancet*, 1944, ii, 5, 659.
32. WEARN, J. T., in discussion to BECK, C. S.: Contusion of the heart, *Jr. Am. Med. Assoc.*, 1935, civ, 114.
- 33a. MASTER, A. M., DACK, S., and JAFFE, H. L.: Activities associated with the onset of acute coronary artery occlusion, *Am. Heart Jr.*, 1939, xviii, 434.
- b. MASTER, A. M.: Letter to the editor, *Jr. Am. Med. Assoc.*, 1942, cxx, 392.
- c. MASTER, A. M.: Letter to the editor, *Jr. Am. Med. Assoc.*, 1945, cxxix, 90.
34. VIKO, L. E.: Personal communication: a 38 year old man was hit by a golf ball over the lower part of the sternum and died 3 days later with signs and symptoms of recent coronary occlusion. A fresh thrombus was found in the anterior descending branch of the left coronary artery. There was no evidence of atheromatous changes in any other vessel examined. See also a similar case, often cited: *Queries and Minor Notes, Jr. Am. Med. Assoc.*, 1933, ci, 1503.
35. WILSON, F. N., HILL, I. G. W., and JOHNSTON, F. D.: The form of the electrocardiogram in experimental myocardial infarction. III. The later effects produced by ligation of the anterior descending branch of the left coronary artery, *Am. Heart Jr.*, 1935, x, 903.
36. WILSON, F. N., JOHNSTON, F. D., and HILL, I. G. W.: The form of the electrocardiogram in experimental myocardial infarction. IV. Additional observations on the later effects produced by ligation of the anterior descending branch of the left coronary artery, *Am. Heart Jr.*, 1935, x, 1025.
37. BARBER, H.: Electrocardiographic changes due to trauma, *Brit. Heart Jr.*, 1942, iv, 83.
38. DAVENPORT, G. L., and MARKLE, P.: The electrocardiogram in stabwounds of the heart, *Jr. Thorac. Surg.*, 1933-34, ii, 376.
39. NOTH, P. H.: Electrocardiographic patterns in penetrating wounds of the heart, *Proc. Am. Fed. Clin. Res.*, 1944, i, 49; *Am. Heart Jr.*, 1946, xxxii, 713.
40. LANGENDORF, R., and GOLDBERG, S.: The electrocardiogram in traumatic pericarditis, *Am. Heart Jr.*, 1942, xxiv, 412.
41. BURCHELL, H. B., BARNES, A. R., and MANN, F. C.: The electrocardiographic picture of experimental localized pericarditis, *Am. Heart Jr.*, 1939, xviii, 133.
42. BAYLEY, R. H., LADUE, J. S., and YORK, D. J.: Electrocardiographic changes (local ventricular ischemia and injury) produced in the dog by temporary occlusion of a coronary artery showing a new stage in the evolution of myocardial infarction, *Am. Heart Jr.*, 1944, xxvii, 164.
43. WHITE, P. D., and GLENDY, R. E., in BRAHDY, L., and KAHN, S.: Trauma and disease, 1937, Lea and Febiger, Philadelphia.

## OXYGEN INHALATION IN THE TREATMENT OF SPONTANEOUS PNEUMOTHORAX \*

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So-called benign, idiopathic, spontaneous pneumothorax has been recognized more and more frequently during the past two or three decades. Inasmuch as this is chiefly an illness of apparently healthy, young males, it is not infrequent in the armed forces. In 1943, there were 873 hospital admissions with a primary diagnosis of spontaneous pneumothorax in the Army in the continental United States.<sup>1</sup> The treatment in common usage consists of bed rest and mild sedation. The average length of hospitalization in the army cases quoted above was 40 days per person.

In addition to the above conservative treatment, other methods have been advocated to hasten reexpansion. Waring<sup>2</sup> recommended injection of a sterile, irritant solution into the pleural cavity to promote adhesions between the parietal and visceral pleura. Welkind and Herman,<sup>3</sup> working chiefly on tuberculous patients with induced pneumothorax, have shown that lavage of the pleural cavity with 100 per cent oxygen considerably hastens reexpansion. From this, they recommend its use in spontaneous pneumothorax and describe one case in which it was used successfully after air aspiration was unsuccessful. Aspiration of air from the pleural cavity has been used by many. Indeed, when pressure pneumothorax exists, it is indispensable and urgent. Philips and Knoepp<sup>4</sup> advocate injection of oxygen intrapleurally, if frequent withdrawal of air is not successful.

Until recently, rupture of a subpleural bleb was believed by many authorities to be the most frequent cause of spontaneous pneumothorax. However, the very thorough studies of Macklin and Macklin<sup>5</sup> suggest pulmonic interstitial emphysema as the etiologic agent in many cases.

Fine, et al.<sup>6</sup> published a description of the inhalation of 95 per cent oxygen to reduce gaseous, intestinal distention. Since then, others have found this method effective. It has also been used to hasten absorption of retained air (chiefly nitrogen) from the cerebrospinal space following pneumoencephalography,<sup>7</sup> and from subcutaneous tissues in subcutaneous emphysema. The principle involved is simply that when blood with the customary small amount of nitrogen in physical solution, comes in contact with an inspired gas that has no nitrogen in it (100 per cent oxygen), rather than with air containing the usual 80 per cent nitrogen, it will give off most of its nitrogen. As the retained gas is chiefly nitrogen, in a relatively short time this is all dissolved into the blood and then given off in the alveolar air, which is almost entirely oxygen.

This rationale suggested itself to the author for application in spontaneous pneumothorax, and its use apparently hastened reexpansion considerably. However, only a single case was available and no conclusions can be drawn. Nevertheless, as this illness is not infrequent in larger Army and Navy hospitals, and since it seems to save many hospital days per patient, it is being suggested for a controlled trial to determine its merit, if any. In addition to increasing the rapidity of resorption of the pneumothorax, the inhalation of 100 per cent oxygen also relieves the apprehension, strained effortful breathing, and pain that is often present during the first day or two of the disease.

\* Received for publication October 2, 1945.

## CASE REPORT

A 28 year old white, male soldier was admitted to the Army Air Forces Station Hospital at Homestead, Florida, on March 31, 1944. He complained of pain in the right shoulder and at the apex of the right lung. The pain was sharp, aggravated by deep breathing and movement of the right upper extremity, and there was an associated dyspnea. The onset was sudden, and occurred early in the morning, while still asleep. There was no previous similar episode and the personal and family history was negative for tuberculosis.

Physical examination revealed a well developed and nourished young man with only mild respiratory distress. Roentgenograms confirmed the physical signs of collapse of the right lung and revealed complete collapse of the upper and lower right lobes and about 80 per cent collapse of the middle lobe. Evidence of an old well-healed childhood tuberculosis was noted on the left. Complete blood count, urinalysis, and sedimentation rate were normal and two sputum specimens were negative for tubercle bacilli.

The patient was kept at complete bed rest and on the second hospital day inhalation of 100 per cent oxygen was started. This was given by oronasal mask (Army Air Forces type A-8B), and continuous flow was used. Oxygen was administered approximately three out of four hours during the first day or two, and then for three or four two-hour periods daily thereafter. This method of oxygen inhalation was continued for 10 days and for the following two days, the "demand" type of mask with a low pressure tank was used for 40 minutes, four or five times daily. Immediately following the administration of oxygen, the amplitude and frequency of respirations decreased, all pain disappeared and the patient felt completely at ease.

A roentgenogram, taken seven days after oxygen therapy was instituted, revealed 95 per cent expansion of the entire right lung, and when the next film was taken, four days later, expansion was complete.

A follow-up study, done 14 months after discharge from the hospital, revealed no pulmonary complication nor recurrence.

## COMMENT

Although published references to the use of 100 per cent oxygen inhalation could not be found, Waring<sup>8</sup> states that: "Inhalation of 100 per cent oxygen has been used on many occasions for the treatment of spontaneous pneumothorax, especially those cases complicated by pulmonary interstitial emphysema. . . ." Lovelace<sup>9</sup> believes that the continuous flow type of mask is preferable to the "demand system," if the flow is kept high enough to avoid emptying the rebreathing bag on inspiration, thus avoiding undue suction. He further recommends interruption of the continuous inhalation of oxygen for five or 10 minutes every three or four hours and suggests that this be limited to a 48 hour period.

## SUMMARY

The inhalation of 100 per cent oxygen in cases of idiopathic, spontaneous pneumothorax is suggested for future controlled trial and its use in one patient is described. The probable advantages are: more rapid reexpansion, relief of dyspnea, apprehension and chest pain, and reduction in time of hospitalization.

## BIBLIOGRAPHY

1. "News and Comment": Bull. U. S. Med. Dept., 1944, lxxxii, 29.
2. WARING, JAMES J.: Bull. Nat. Research Council, July, 1944, quoted in "News and Comment," Bull. U. S. Army Med. Dept., 1944, lxxxii, 29.

3. WELKIND, A., and HERMAN, M.: Rapid reëxpansion of lungs; pleural lavage with oxygen: further studies, *Quart. Bull. Sea View Hosp.*, 1941, vi, 208-224.
4. PHILIPS, J. R., and KNOEPP, L. F.: Spontaneous pneumothorax, *Dis. Chest*, 1940, vi, 243-248.
5. MACKLIN, M. T., and MACKLIN, C. C.: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment, *Medicine*, 1944, xxiii, 281-359.
6. FINE, J., BANKS, B. M., SEARS, J. B., and HERMANSON, L.: Treatment of gaseous distension of intestine by inhalation of 95 per cent oxygen. Description of apparatus for clinical administration of high oxygen mixtures, *Ann. Surg.*, 1936, ciii, 375-387.
7. SCHWAB, R. S., FINE, J., and MIXTER, W. J.: Reduction of postencephalographic symptoms by inhalation of 95 per cent oxygen, *Arch. Neurol. and Psychiat.*, 1937, xxxvii, 1271-1282.
8. WARING, JAMES J., Denver, Colorado, Personal communication.
9. LOVELACE II, W. RANDOLPH, Col. M.C., Personal communication.

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## A FATAL CASE OF SCRUB TYPHUS INTRODUCED INTO THE UNITED STATES \*

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THE facility and speed of air evacuation may result in the return of personnel who are in the incubation stages of tropical diseases. Medical officers, public health physicians and civilian practitioners in general are becoming increasingly conscious of the presence of protozoan and helminthic diseases among travelers who have returned to the temperate zone. This case calls attention to the need for the consideration of the scrub typhus group of rickettsial diseases in the fevers of troops who have recently returned from endemic areas.

### CASE REPORT

The patient was a 32 year old pathologist who had served 25 months in the China-Burma-India Theater of Operations during which time he was frequently and closely in contact with scrub typhus, especially at the autopsy table. He was flown from the CBI Theater on August 3, 1945 for reassignment in the United States and reached this station August 11, 1945 after eight days of travel.

On leaving Karachi, India, the patient for the first time complained of headache, malaise and unwonted listlessness and apathy. As the flight continued, the headache became unrelenting, particularly over the retro-orbital region, and was associated with persistent nausea, intermittent vomiting and mental confusion. The symptoms became increasingly severe; the nausea and vomiting were so intense that the patient abstained from food and drink; the periods of mental wandering became more frequent and marked deafness and low-grade fever developed.

On arriving at this station, the Medical Officer was promptly hospitalized. The impaired bilateral auditory acuity, utter exhaustion, disorientation, perplexity, lassitude and strange euphoria were prominent. Dehydration was severe; the tongue was exceedingly dry, swollen, furrowed and dull, the lips fissured and covered with sordes,

\* Received for publication January 26, 1946.

From Medical Service, Station Hospital, Camp Kilmer, N. J.



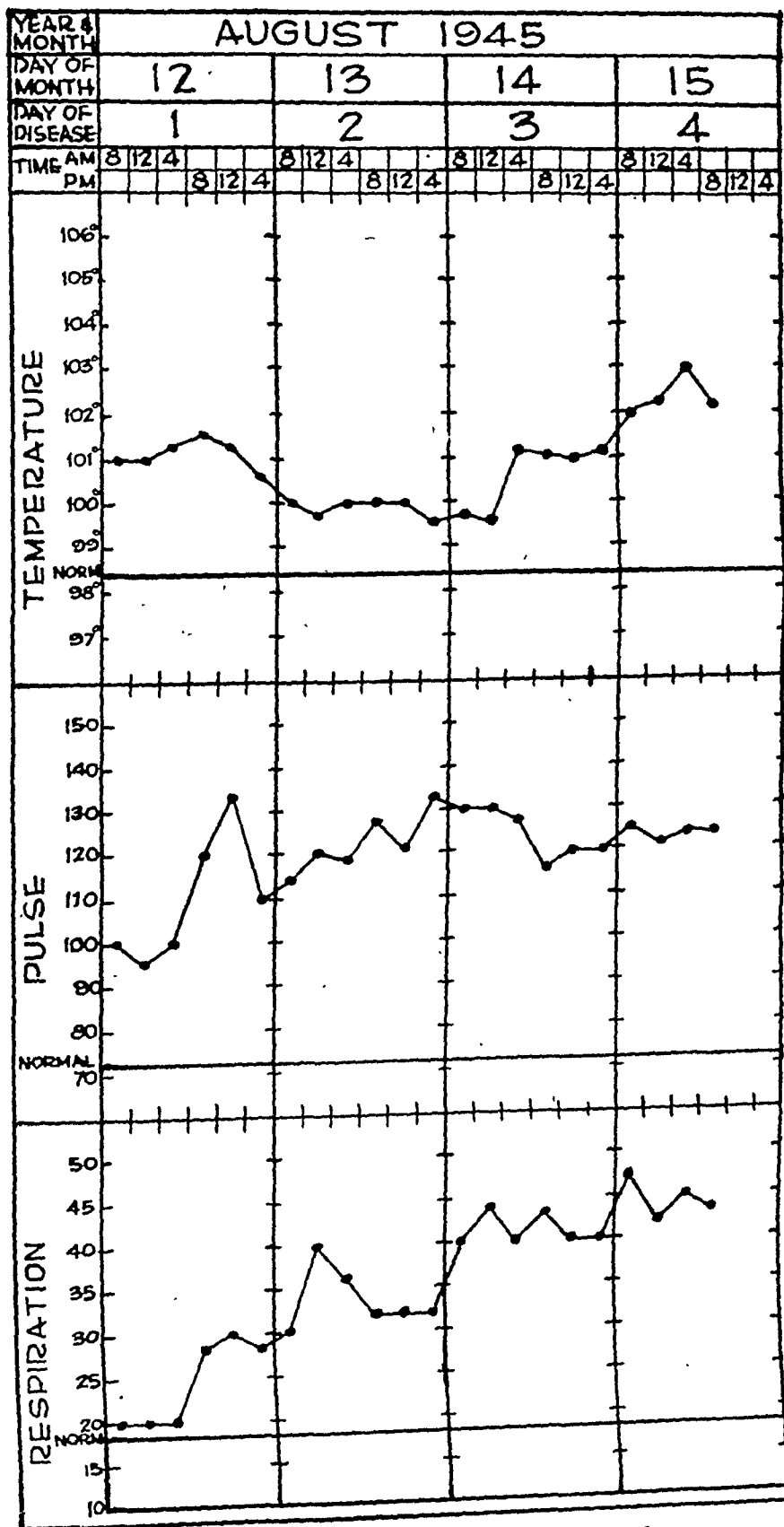
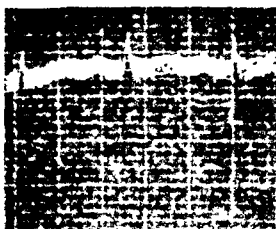


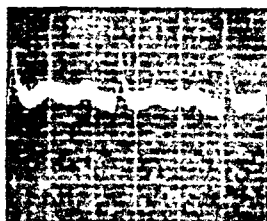
FIG. 1. Clinical course of fatal case of scrub typhus.

the skin turgor greatly diminished. The eyes revealed characteristic bilateral conjunctivitis. Respirations were rapid, 28 per minute and shallow. The lungs were normal to percussion and auscultation. The heart sounds were of poor quality and rapid, 140 per minute. Blood pressure was 102 mm. of mercury systolic and 70 mm. diastolic. A discrete pink maculo-papular eruption was present over the trunk and abdomen. Search for an eschar and regional adenopathy was negative. The liver and spleen were not palpable.

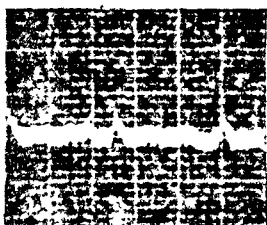
Lead 1



Lead 2



Lead 3



Lead 4

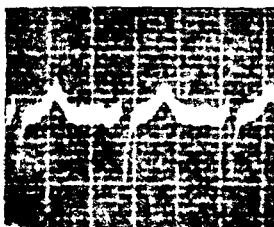


FIG. 2. Electrocardiogram taken August 13, 1945. The rate is 120. The QRS complexes are of low amplitude and slurred, the T waves are of low voltage.

Urinalysis disclosed proteinuria (3 plus), specific gravity 1.015, no sugar, blood or bile. Many granular casts and white blood cells were present. The blood urea nitrogen was 75 mg. per 100 c.c. The hemogram was not unusual. White blood cells were 11,850, hemoglobin 84 per cent, neutrophils 79 per cent, lymphocytes 17 per cent, monocytes 1 per cent and eosinophiles 3 per cent. Smears for malaria were negative. The spinal fluid was normal except for elevation of protein to 100 mg. per 100 c.c. Stool examination was essentially negative. Roentgenograms of the chest showed exaggeration of markings of right root suggesting an atypical pneumonia or congestion. The heart contour was normal.

Supportive and symptomatic therapy was promptly instituted. The azotemia and dehydration were combated by the restoration of adequate fluid balance with dextrose-saline infusions. Sedation, maximum bed rest and oxygen were employed to counteract pulmonary and cardiac complications.

The clinical course was brief. The temperature varied from 101° to 103° F. accompanied by persistent sinus tachycardia (120 to 130 per minute) and tachypnea (28 to 50 per minute) (figure 1). The hypotension and poor heart sounds persisted. The venous pressure never exceeded 120 mm. of water. The breath sounds became suppressed posteriorly. Generalized muscle twitching became quite evident and delirium more marked. The electrocardiogram corroborated the clinical impression of severe myocarditis (figure 2).

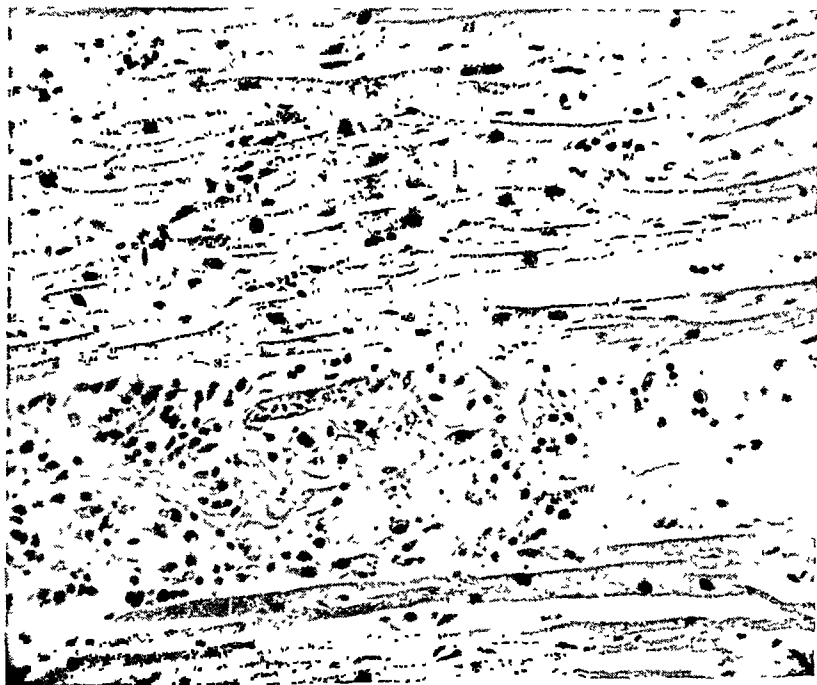


FIG. 3. Section of myocardium showing edema and diffuse interstitial cellular infiltration. Giemsa  $\times 178$ .

Serum was examined August 14, 1945 for antibodies in the Weil-Felix test by the Division of Virus and Rickettsial Diseases of the Army Medical Center of the Army Medical School and the following results were obtained:

Proteus OX-19 negative  
Proteus OX-2 negative  
Proteus OX-K complete 1/160, partial 1/640

Serum obtained eight hours later was examined by the Second Service Command with results as follows:

Proteus OX-19 negative  
Proteus OX-2 negative  
Proteus OX-K positive 1/1,280

Fatal pulmonary edema occurred August 16, 1945 and autopsy was performed the same morning. The right lung weighed 1,060 grams and exhibited consolidation of the lateral half of the lower lobe. Microscopically, the pleura showed no attached

exudate. The cortical (sub-pleural) zone presented areas of vesicular emphysema. More deeply the acini were filled with albuminous material including a great many swollen lightly pigmented macrophages. The bronchioles were compressed. The heart weighed 370 grams. The entire myocardium was soft and flabby. On the upper surface of the mitral valve were minute firm vegetations extending into the left auricle. Microscopically, the epicardium was thin and showed interstitial cellular infiltration. The small coronary branches included in the sections studied displayed normal walls. The muscle fibers of the myocardium were broad and the striae well differentiated. Throughout the muscle wall of the heart there was edema and diffuse interstitial cellular infiltration consisting of plasma cells, small lymphocytes, scattered larger cells with acidophilic cytoplasm, possibly cells of the Anitschkow myocyte type (figure 3). The

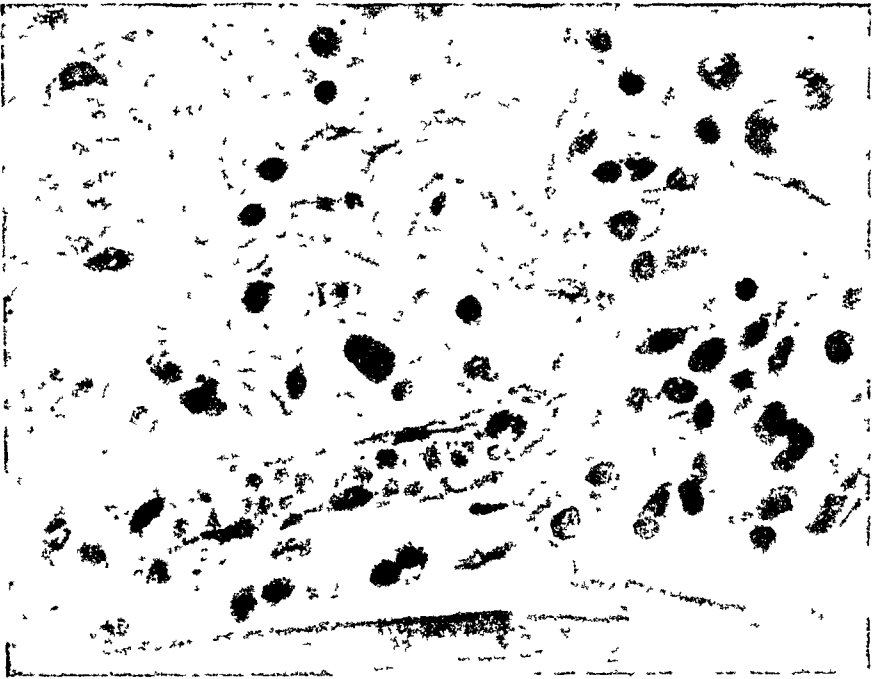


FIG. 4. Interstitial cellular infiltrate of myocardium showing numerous massed cells presenting plump granules. Giemsa  $\times 563$

anterior cusp of the mitral valve revealed a thin base and thickened terminal segment of the valve. There was no increase in vascularity or cellular reaction. The "verrucosity" noted was regarded as "marantic," terminal, and not organic. The mural endocardium was thin and showed edema. Sections of the heart stained by Giemsa were particularly interesting. The interstitial cellular infiltrate included fairly numerous massed cells presenting plump granules, staining a plum color. A few cells regarded as pericytes (adventitial cells) included fairly dense clumps of very delicate cocco-bacillary forms staining a light blue. The cocco-bacillary forms resembled rickettsia (figure 4). Cells presenting rickettsia-like bodies are extremely rarely encountered in the type of sections studied. The spleen weighed 460 grams, was enlarged and extremely soft. The architecture was completely obliterated, and only a semi-fluid material remained within the capsule. Microscopic examination of a relatively intact small accessory spleen showed the trabeculae widely separated. The red pulp displayed a loss of normal architecture; the sinusoids were filled with cells of the granulocytic series showing a shift to the left. The liver weighed 2,290 grams and

appeared extremely congested. Microscopically, the architecture was preserved. There was venous congestion and congestion of the sinusoids. The sinusoids included many white blood cells, granulocytes and cells of the lymphocytic series. The liver cells were compressed, finely granular and displayed varying degrees of fat infiltration. The triads showed congestion of the terminal branches of the portal vein; one portal vein included a thrombus consisting of closely clumped coccal forms without cellular reaction. The kidneys appeared congested. Microscopically, the renal architecture was preserved. The cells lining the tubuli contorti were swollen and finely granular; the lumen of these tubules contained a finely granular acellular detritus. The terminal brush formation of the cells lining the convoluted tubules was fairly well preserved. There was ischemia, postmortem degeneration and cloudy swelling. The brain, grossly, showed moderate injection of the pial vessels. Microscopically, the sub-arachnoid showed congestion. The sub-arachnoid and the sub-pial zone displayed diffuse cellular infiltration consisting of cells of the lymphocytic series, some plasma cells and a few granulocytes. The cerebral cortex showed slight edema. The findings were those of congestion and slight cellular infiltration.

### DISCUSSION

Scrub typhus or tsutsugamushi fever is an acute febrile disease caused by *Rickettsia tsutsugamushi* (*Rickettsia orientalis*) and closely resembles the other members of the group of rickettsial infections.

This case emphasizes the salient feature of the disease. Air evacuation of the subject of this report to the United States from a highly endemic focus returned him within the incubation period of seven to 21 days. The absence of a primary eschar is common in Burma and India as opposed to its characteristic presence in most Asiatic regions. The clinical picture in this case embraced the characteristic findings of severe scrub typhus. Headache, malaise, nausea and deafness were present early as was mental cloudiness of increasing severity. Cyanosis, tachypnea, tachycardia and hypotension attested to the complicating atypical pneumonia and myocarditis. The euphoria, delirium, muscular twitchings and coma were evidence of dreaded central nervous system involvement. Histopathologic examinations corroborated the pathologic lesions described by Lipman et al.

As far as can be determined, this is the first reported case of scrub typhus introduced into the United States from an overseas theater.

Modern communication is bringing the diagnostic problems of tropical diseases to this country; a careful history, suspicion and awareness of their possibility will meet the diagnostic challenge successfully.

### BIBLIOGRAPHY

1. LIPMAN, BERNARD L., CASEY, ADRIAN V., BYRON, ROBIN A., and EVANS, EDWIN C.: Scrub typhus, War Med., 1944, vi, 5.

## EDITORIAL

### ON THE ETIOLOGY OF CANCER—COCARCINOGENIC AGENTS

DURING the fifteen years that have elapsed since the isolation of the carcinogenic substance benzpyrene from coal tar (Cook, Hewett, Hieger<sup>1</sup>), a relatively large number of substances have been tested for their cancer-producing potentialities. Cook and Kennaway<sup>2,3</sup> surveyed the most important work up until 1938 and listed 860 papers in the bibliography. Over 1,000 compounds have been listed in a recent revision of Hartwell's extensive survey<sup>4</sup> of compounds that have been tested for carcinogenicity. Two hundred and sixty-four, or approximately one-fourth of the substances tested, have been shown to induce cancer. In the early part of this work on carcinogenic agents, considerable stress was laid on chemical structure. The possibility of establishing any chemical or standard pattern for carcinogenicity has gradually faded as the list of chemicals that have been successfully used to induce cancer has grown longer. This list now includes not only the potent steroidal compounds; methylcholanthrene, benzpyrene and dibenzanthracene; but such heterogeneous substances as carbon tetrachloride, urethane (to induce lung tumors), butter yellow or dimethylamino azobenzene (hepatomas), estrogens (breast cancer and uterine cancer), amino fluorene, beta naphthalamine, scarlet red dye, etc. Finally, but not less astonishing, 25 per cent glucose solutions have been used to induce cancer in rats.<sup>5</sup>

When we add to this list of over 250 chemicals the four regions of the electromagnetic spectrum that have been found to be carcinogenic (gamma rays, roentgen-rays, ultraviolet light, and heat), it makes an impressive list of agents for use in experimental cancer induction. As this list grows, the search for the cause or causes of cancer becomes not simpler, but more and more complex. There are many who think that the cause of neoplastic diseases will finally prove to be not a single factor, but that the causes will be as diverse as the neoplasms and the tissues affected.

The ease with which it is possible to induce cancer experimentally in mice and rats has led to the assumption that these agents would be equally carcinogenic in all other species. It is important to realize that they are not. As a matter of fact they have not been adequately tested even in such com-

<sup>1</sup> COOK, J. W., HEWETT, C. L., and HIEGER, I.: The isolation of a cancer-producing hydrocarbon from coal tar. Parts I, II and III, *Jr. Chemical Soc.*, 1933, p. 395.

<sup>2</sup> COOK, J. W., and KENNAWAY, E. L.: Chemical compounds as carcinogenic agents. First supplementary report: Literature of 1937, *Am. Jr. Cancer*, (Bibliography), 1938, xxxiii, 50.

<sup>3</sup> COOK, J. W., and KENNAWAY, E. L.: Chemical compounds as carcinogenic agents. Second supplementary report: Literature of 1938 and 1939, *Am. Jr. Cancer*, 1940, xxxix, 381, 521.

<sup>4</sup> HARTWELL, J. L.: Survey of compounds which have been tested for carcinogenic activity, *Nat. Inst. Health, Nat. Cancer Inst., U. S. Pub. Health Service, Bethesda, Md.*, 1941.

<sup>5</sup> NONAKA, T.: The occurrence of subcutaneous sarcomas in the rat after repeated injections of glucose solution, *Gann*, 1938, xxxii, 234.

mon laboratory animals as dogs, cats and guinea pigs. A summary<sup>6</sup> of the data tabulated in Hartwell's survey of carcinogenic compounds reveals this in a striking way. According to this summary approximately 9,000 or 42 per cent of 21,000 mice treated with one of the three most potent carcinogens (1,2,5,6 dibenzanthracene; 3,4 benzpyrene; 20 methylcholanthrene) developed tumors. Four thousand and eight hundred rats were treated with the same substances and 33 per cent or 1,600 developed tumors. Five hundred and twenty-nine rabbits yielded only 47 tumors or about 9 per cent; only 9 of 110 guinea pigs or 8 per cent developed tumors. It is remarkable that only 13 dogs are included in this comprehensive survey of the literature and no tumors resulted. Cats and monkeys were not even mentioned, so it would appear that these agents had not been tried at all in these animals. This is probably a false impression for cats and monkeys have doubtless been treated with these carcinogenic agents but the results of this work have failed to appear because of the general and unfortunate tendency to omit the publication of negative results. More recently there have appeared some brief notes on the drastic but unsuccessful attempts to induce cancer in monkeys with large doses of estrogens,<sup>7,8</sup> methylcholanthrene,<sup>8</sup> and other agents.

It is evident that mice and rats exhibit a relatively great but variable sensitivity to the cancer-producing chemicals while other animals are more resistant. An attempt to discover the cause of this sensitivity led to the concept that the unique porphyrin metabolism which these rodents exhibit might be related to their high sensitivity.<sup>6</sup> The search for porphyrins in the organs and tissues of human subjects that show a high cancer incidence revealed that some of these organs and tissues (cervix of the uterus, skin of the face) are frequently subjected to excessive and abnormal concentrations of porphyrins.<sup>6,9,10,11</sup> Porphyrins have also been used to increase the sensitivity of certain mice of so-called resistant strains. The porphyrins, when administered alone, have no carcinogenic action. When administered concurrently, however, they decrease the latent period for methylcholanthrene-induced tumors and ultraviolet light-induced tumors.<sup>6</sup> They also appear to increase the sensitivity of tissues to the action of estrogenic compounds.<sup>6</sup> Some of the porphyrins (protoporphyrin, mesoporphyrin, deuteroporphyrin) have therefore been classified as naturally occurring *cocarcinogenic* compounds.

<sup>6</sup> FIGGE, F. H. J.: The relationship of pyrrole compounds to carcinogenesis, A.A.A.S. Research Conference on Cancer, edited by F. R. Moulton, Science Press Printing Co., Lancaster, Pa., 1945, 117-128.

<sup>7</sup> ENGLE, E. T., KRAKOWER, C., and HAAGENSEN, C. D.: Estrogen administration to aged female monkeys with no resultant tumors, *Cancer Res.*, 1943, iii, 858-866.

<sup>8</sup> ALLEN, E.: Report of activities during 1940 (p. 8), Report of activities during 1941 (p. 24), International Cancer Research Foundation.

<sup>9</sup> FIGGE, F. H. J.: Fluorescence studies on cancer. I. Porphyrin metabolism, Harderian gland fluorescence, and susceptibility to carcinogenic agents, *Cancer Res.*, 1944, iv, 465-470.

<sup>10</sup> JONES, E. G., FIGGE, F. H. J., and HUNDLEY, J. M.: Fluorescence studies on cancer. II. The red fluorescence of the genitalia of women, *Cancer Res.*, 1944, iv, 472-482.

<sup>11</sup> FIGGE, F. H. J., JONES, E. G., and WOLFE, G. F.: Fluorescence studies on cancer. III. The extraction and identification of porphyrins from the red-fluorescent exudates on the genitalia of women, *Cancer Res.*, 1944, iv, 483-486.

The principle of cocarcinogenic action is not a new one. The term was first introduced by Shear<sup>12, 13</sup> to describe a non-carcinogenic fraction of coal tar that appeared to augment the activity of benzpyrene. This served to explain why the original tar was much more active than the purified benzpyrene which was extracted from it. The cocarcinogenic fraction in tar was not isolated or characterized and it is of interest in this connection that many coals and shale oils contain porphyrins. The term cocarcinogenic was next adopted by Berenblum<sup>14</sup> to describe the action of croton oils and resins. He found that croton oil alone was not carcinogenic but when this oil or resin extract was administered along with a very low, almost sub-carcinogenic, concentration of benzpyrene in acetone this resulted in a greatly increased carcinogenic potency. The cocarcinogenic action was not related to the irritant properties of croton oil. Other vesicants and irritants such as mustard gas and turpentine were not found to be cocarcinogenic when tested under identical conditions. Berenblum therefore defined cocarcinogenic action as the augmentation of carcinogenesis by a non-carcinogenic agent.

More recently, Bielschowsky<sup>15</sup> has described another type of cocarcinogenic action. He observed over 100 neoplasms in 93 Wistar rats which had been fed 4 milligrams of 2-acetylaminofluorene. The most of these tumors involved the liver, mammary gland and the external acoustic meatus. When he gave 2-acetylaminofluorene in combination with allyl-thiourea he observed a high incidence of adenocarcinoma of the thyroid glands.<sup>16</sup> Thus a compound of thiourea which normally produces only a hyperplasia of the thyroid gland when administered along with aminofluorene gave rise to neoplasms of the thyroid gland. In other words, a relatively weak non-specific carcinogen was converted to a potent one with more specific action. In this case, the specificity or site of action appeared to be controlled by the cocarcinogen.

The practical significance of these demonstrations of cocarcinogenic agents is that we must begin to consider not only the action of a single substance but also the influence it will have when administered along with other substances or with substances such as porphyrins which may be present naturally. In the examples cited, the carcinogenic combinations of substances have always included one substance which, by itself, acted as a weak carcinogenic agent and another substance, the cocarcinogen, which augmented the action of the so-called carcinogen. So far there have been no reports on cancer production by a combination of two substances which when administered singly never produce cancer.

<sup>12</sup> SHEAR, M. J.: Studies in carcinogenesis: methyl derivatives of 1:2-benzanthracene, *Am. Jr. Cancer*, 1938, xxxiii, 499-537.

<sup>13</sup> SALL, R. D., and SHEAR, M. J.: Studies on carcinogenesis. XII. Effect of the basic fraction of creosote oil in the production of tumors in mice by chemical carcinogens, *Jr. Nat. Cancer Inst.*, 1940, i, 45-55.

<sup>14</sup> BERENBLUM, I.: The cocarcinogenic action of croton resin, *Cancer Res.*, 1941, i, 44-48.

<sup>15</sup> BIELSCHOWSKY, F.: Distant tumors produced by 2-amino and 2-acetyl-amino-fluorene, *Brit. Jr. Exper. Path.*, 1944, xxv, 1-4.

<sup>16</sup> BIELSCHOWSKY, F.: Tumors of the thyroid produced by 2-acetyl-amino-fluorene and allyl-thiourea, *Brit. Jr. Exper. Path.*, 1944, xxv, 90-94.



Quite recently, however, a new hypothesis<sup>17</sup> has been introduced which may eventually cause us to modify our definition of a carcinogenic agent. According to this hypothesis the action of carcinogenic compounds depends on their ability to convert energy derived from cosmic and similar penetrating radiations into energy which induces cancer. In support of this hypothesis, lead plates  $\frac{1}{4}$ " to  $\frac{1}{2}$ " thick, which intensify the effect of cosmic radiation, accelerate the rate of tumor induction by methylcholanthrene. Lead plates have also been used to increase the incidence of spontaneous mammary carcinomas in mice; and shielding from cosmic radiation showers decreased the spontaneous cancer incidence in mice of the same strain.<sup>18</sup>

If the hypothesis that cosmic radiation is a primary factor in carcinogenesis is true, then these diverse substances would not be carcinogenic in the absence of cosmic radiation and they would have to be regarded not as carcinogens but rather as cocarcinogens. It is doubtful, however, that cosmic radiation could produce cancer in the absence of these chemical agents, otherwise cancer would be more widespread and abundant than it is. We would thus have a situation in which a low intensity non-carcinogenic form of energy is converted into a carcinogenic form of energy by cocarcinogens which we now erroneously call carcinogenic agents. The possible augmentation of the action of this energy by substances such as porphyrins and croton oil would require the inclusion of additional cocarcinogens. According to this concept of cocarcinogenic action, cancer would be caused not by a single substance but by two, three or more non-carcinogenic interdependent agents.

F. H. J. FIGGE

<sup>17</sup> FIGGE, F. H. J.: Cosmic radiation and cancer, *Science*, 1947, cv, 323-325.

<sup>18</sup> EUGSTER, I., and HESS, V. F.: *Weltraumstrahlung und ihre biologische Wirkung*, 1940, Orell Füssli Verlag, Zurich-Leipzig.

## REVIEWS

*The Treatment of Peptic Ulcer.* By GEORGE J. HEUER, M.D., assisted by CRANSTON HOLMAN, M.D., and WILLIAM A. COOPER, M.D. 118 pages; 16 × 23.5 cm. J. B. Lippincott Co., Philadelphia. 1944. Price, \$3.00.

In this period in which the introduction of vagotomy as a surgical procedure in the treatment of peptic ulcer is under such active discussion, careful analyses of the results of surgical treatment by other methods are of timely interest. Particularly valuable is the reminder that the value of any one method can only be assessed after study of a considerable group of cases followed for from five to ten years.

Dr. Heuer's study, published in 1944, is based upon the follow-up of 1204 patients admitted to the New York Hospital and its Outpatient Department between 1932 and 1942 of whom 39.2 per cent were treated surgically within the period named. Of 732 patients whose initial treatment was medical the results were considered satisfactory in only 54.9 per cent. On the other hand the mortality due to ulcer in this group was 3.5 per cent.

It is interesting to note that the operative mortality plus the late mortality (due to ulcer causes) of cases treated by gastro-enterostomy was 5.9 per cent; but that the satisfactory results were assessed as 73.6 per cent of 201 cases.

A similar comparison of the medically treated cases with those treated by gastric resection shows that in the latter the total mortality (operative and later from ulcer causes) was 7.7 per cent and the percentage of satisfactory results was 83 per cent in 142 cases.

These figures then suggest that in peptic ulcer a higher percentage of satisfactory results is obtained by standard surgical procedures (exclusive of vagotomy) but at the expense of a distinct increase in the total mortality rate among those so treated above that observed in the medically treated cases. The significance of these findings, however, must be qualified by the fact that the surgically treated cases were a selected group which included a much higher percentage of severe or complicated cases than those treated exclusively by medical measures.

It would have been interesting if the author had drawn a comparison between the total mortality in the group who remained on medical treatment after having been advised to submit to operation and the group who because of a similarly unsatisfactory result from medical treatment were operated upon.

The reader will find far more in this little book than such general statistics on results as are referred to above. There are interesting discussions on the rôle of surgery in hemorrhage; on the value of gastro-enterostomy which the author feels still has a distinct place; on the results of operations for perforation; on the question of malignant changes in gastric ulcer.

It is not often that one encounters in any special field a more helpful monograph.  
M. C. P.

*Endocrine Function of the Hypophysis.* By HARRY B. FRIEDGOOD, M.D.; Edited by HENRY A. CHRISTIAN, M.D., F.A.C.P. 828 pages; 16 × 24 cm. Oxford University Press, New York. 1946. Price, \$4.50.

Although this is described in the preface as a monograph written for the physician, surgeon and investigator, its chief value would be to the investigator for whom it presents a comprehensive discussion of known and supposed hypophyseal functions with an unusually extensive bibliography. The physician or surgeon will find ade-

quate descriptions of acromegaly, gigantism and dwarfism, but the spirit of the book is more investigative than clinical.

The first part of the book presents a detailed description of the anatomy, embryology and phylogeny of the hypophysis. Part two considers the cytophysiology and biochemistry of the anterior lobe of the hypophysis. The following two sections consider the factors affecting growth and the clinical disorders of growth. Part five discusses the functions of the neurohypophysis. The bibliographies attest to the extensive literature which Dr. Friedgood has reviewed in preparing this monograph. The accessibility of the material would be increased by a more detailed index.

J. Z. B.

*Government in Public Health.* By HARRY S. MUSTARD, B.S., M.D., LL.D. 219 pages; 21.5 × 14.5 cm. The Commonwealth Fund, New York, N. Y. 1945. Price, \$1.50.

Though it was published in 1945, this small volume deserves review at this date in order to bring it again to the attention of physicians. The rapid extension of the field of public health is the most important trend in modern medicine. The historical development of this movement in the United States and its present status should be known to every physician and should be part of the education of every medical student. The character of future developments in this field is dependent upon an informed medical profession.

Dr. Mustard's book admirably fulfills its purpose of a critical but dispassionate survey of the development at local, state and federal levels of our present program of tax supported public health and medical care. He points out the importance of the practicing physician in public health. He discusses the relationship of voluntary medical programs and institutions to those under governmental control.

Though dealing with a subject which is controversial, the author keeps his book above the level of propaganda. One feels how much condensation and selection from a wealth of personal experience and historical research have been necessary to make possible the presentation in this small volume of such a factual, interesting and stimulating account of a complex problem.

M. C. P.

### BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Acute Infectious Fevers (The).* By ALEXANDER JOE, D.S.C., M.D., F.R.C.P., D.P.H., Medical Superintendent, City Hospital, Edinburgh; Lecturer on Infectious Diseases, University of Edinburgh, etc. 276 pages; 22.5 × 13.5 cm. 1947. The Blakiston Company, Philadelphia. Price, \$4.50.

*Color Atlas of Hematology*, with Brief Clinical Descriptions of Various Diseases. By ROY R. KRACKE, M.D., Dean and Professor of Clinical Medicine, Medical College of Alabama. 204 pages; 24 × 16 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$5.00.

*Diseases of the Chest*, with Emphasis on X-Ray Diagnosis. By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital and Country Sanatorium, New York, etc. *Principles of Surgical Treatment (The).* By MORRIS RUBIN, B.A., M.D., Assistant Visiting Surgeon, Triboro Hospital and Morrisania City Hospital, New York, etc. 685 pages; 26.5 × 18.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$12.00.

- Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner.* (2nd Edition.) Edited by GARFIELD G. DUNCAN, M.D., Director of Medical Division, Pennsylvania Hospital, etc., with contributions by various others. 1045 pages; 25 × 17 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Gastritis.* By RUDOLF SCHINDLER, M.D., F.A.C.P., Clinical Professor of Internal Medicine (Gastroenterology), College of Medical Evangelists, Los Angeles, etc. 462 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, \$10.00.
- Genetics, Medicine and Man.* By H. J. MULLER of Indiana University; C. C. LITTLE of the Roscoe B. Jackson Memorial Laboratory; LAURENCE H. SNYDER of The Ohio State University. 158 pages; 23.5 × 15.5 cm. 1947. Cornell University Press, Ithaca, New York. Price, \$2.25.
- Human Gastric Function. An Experimental Study of a Man and His Stomach.* (2nd Edition.) By STEWART WOLF, M.D., Assistant Professor of Medicine, Cornell University Medical College, and HAROLD G. WOLFF, M.D., Associate Professor of Medicine, Cornell University Medical College. 262 pages; 24.5 × 16 cm. 1947. Oxford University Press, New York. Price, \$5.00.
- Medical Aspects of Growing Old.* By A. T. TODD, M.B. (Edin.), M.R.C.P. (Lond.), Honorary Physician, Bristol Royal Infirmary. 164 pages; 22.5 × 14.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, \$3.50.
- Methods of Vitamin Assay.* Prepared and edited by The Association of Vitamin Chemists, Inc. 189 pages; 23.5 × 15.5 cm. 1947. Interscience Publishers, Inc., New York. Price, \$3.50.
- Penicillin Therapy.* Including Streptomycin, Tyrothricin and Other Antibiotic Therapy (2nd Edition). By JOHN A. KOLMER, M.S., M.D., Dr. P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple University. 339 pages; 25.5 × 17.5 cm. 1947. D. Appleton-Century Company, New York-London. Price, \$6.00.
- Peripheral Vascular Diseases (Angiology)* (2nd Edition). By SAUL S. SAMUELS, A.M., M.D., Consulting Vascular Surgeon, Long Beach Hospital, etc. 85 pages; 22 × 14 cm. 1947. Oxford University Press, New York. Price, \$2.50.
- Principles and Practice of Medicine (The)* (16th Edition). CHRISTIAN-OSLER. 1539 pages; 24.5 × 16 cm. 1947. D. Appleton-Century Company, Inc., New York. Price, \$10.00.
- Pulmonary Tuberculosis: A Handbook for Students and Practitioners.* By R. Y. KEERS, M.D., M.R.C.P., (Edin.), F.R.F.P.S. (Glas.), Medical Director, Red Cross Sanatoria of Scotland, etc., and B. G. RIGDEN, M.R.C.S. (Eng.), L.R.C.P. (Lond.), First Assistant Medical Officer, Red Cross Sanatoria of Scotland, etc., with a Foreword by F. H. YOUNG, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H., Physician, Brompton Hospital for Consumption and Diseases of the Chest, etc. 227 pages; 19 × 12.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, \$5.00.
- Recopilacion de Leyes, Reglamentaciones, Decretos y Resoluciones.* Ministerio del Interior, Republica Argentina. 928 pages; 26.5 × 18 cm. 1945. Ministerio del Interior—La Camara de Diputados, Buenos Aires, Argentina.

- Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions.* By EDITH L. POTTER, M.D., Ph.D., Assistant Professor of Pathology, Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-In Hospital. 344 pages; 21 × 14.5 cm. 1947. Year Book Publishers, Chicago. Price, \$5.50.
- Textbook of Medicine (A) (7th Edition).* Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; with the assistance of WALSH McDERMOTT, M.D., Associate Professor of Medicine, Cornell University Medical College; Associate Editor for Diseases of the Nervous System, HAROLD G. WOLFF, M.D., Associate Professor of Neurology, Cornell University Medical College. 1730 pages; 26 × 18.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$10.00.
- Textbook of Medicine (8th Edition).* By Various Authors. Edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. Oxon., F.R.C.P., Physician to Guy's Hospital, London. 1170 pages; 22.5 × 14.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, \$8.00.
- Textbook of Pathology (A) (6th Edition).* By E. T. BELL, M.D., Professor of Pathology, University of Minnesota. Contributors: B. J. CLAWSON, M.D., Professor of Pathology, University of Minnesota; J. S. McCARTNEY, M.D., Associate Professor of Pathology, University of Minnesota. 910 pages; 24 × 15.5 cm. 1947. Lea & Febiger, Philadelphia. Price, \$10.00.
- Tuberculosis as It Comes and Goes (2nd Edition).* By EDWARD W. HAYES, M.D., F.A.C.P., Associate Professor of Tuberculosis, College of Medical Evangelists, etc., with Chapters by LAURENCE de RYCKE, Ph.D. 220 pages; 23 × 15 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$3.75.

# COLLEGE NEWS NOTES

## ADDITIONAL LIFE MEMBERS

The College takes pleasure in announcing that the following Fellows became Life Members of the College as of the dates given:

Dr. Ralph H. Homan, El Paso, Tex., May 22, 1947  
Dr. Nathan Worth Brown, Toledo, Ohio, May 23, 1947  
Dr. George Miller Jones, Dallas, Tex., May 24, 1947  
Dr. Paul Gross, Glenshaw, Pa., May 24, 1947  
Dr. Verne S. Caviness, Raleigh, N. C., May 28, 1947  
Dr. Harold J. Starr, Chattanooga, Tenn., May 29, 1947  
Dr. Christopher J. McLoughlin, Atlanta, Ga., June 2, 1947  
Dr. Clyde L. Mattas, Scranton, Pa., June 3, 1947  
Dr. Roger S. Whitney, Colorado Springs, Colo., June 4, 1947  
Dr. Louis A. Scarpellino, Kansas City, Mo., June 12, 1947

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## AMERICAN COLLEGE OF PHYSICIANS WILL OFFER POSTGRADUATE COURSES DURING AUTUMN, 1947

More than 1,200 physicians registered in the postgraduate courses offered by the American College of Physicians during the past year. The popularity of these courses is growing and the practicability is being rapidly recognized.

While it is the preference of the Advisory Committee on Postgraduate Courses that the groups be limited to small numbers, it is necessary at the present time, in many instances, to admit larger groups because of the limited number of these short, intensive courses that are available.

Beginning with the autumn, 1947 courses, the tuition fees will be as follows:

(a) For small, limited, clinical courses:

Members of the College (per week), \$60.00  
Non-Members (per week), \$120.00

(b) Regular courses:

Members of the College (per week), \$30.00  
Non-Members (per week), \$60.00

The College will retain, to help defray administrative costs and other expenses, \$5.00 of each candidate's fee and will remit the balance to the Director or institution where the course is given.

## Proposed Schedule of Courses, Autumn, 1947

No.

- 1 INTERNAL MEDICINE—University of Pittsburgh School of Medicine, Pittsburgh;  
Dr. R. R. Snowden, Director—two weeks, Sept. 1–13; Fee—A.C.P. Members,  
\$60.00; Non-Members, \$120.00
- 2 PSYCHOSOMATIC MEDICINE—University of Colorado School of Medicine, Denver;  
Dr. Franklin G. Ebaugh, Director—two weeks, Sept. 8–20; Fee—A.C.P.  
Members, \$60.00; Non-Members, \$120.00
- 3 HEMATOLOGY—BLOOD DISORDERS—Thorndike Memorial Laboratory, Boston City  
Hospital; Dr. William B. Castle, Director—one week, Oct. 13–18; Fee—  
A.C.P. Members, \$30.00; Non-Members, \$60.00

- 4 **PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE**—University of Pennsylvania School of Medicine, Philadelphia; Dr. Julius H. Comroe, Jr., Director—one week, Oct. 20–25; Fee—A.C.P. Members, \$30.00; Non-Members, \$60.00
- 5 **INTERNAL MEDICINE**—University of Wisconsin Medical School, Madison; Dr. William S. Middleton, Director—two weeks, Nov. 3–14; Fee—A.C.P. Members, \$60.00; Non-Members, \$120.00
- 6 **ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE**—Massachusetts General Hospital, Boston; Dr. Paul D. White, Director—two weeks, Nov. 10–22; Fee—A.C.P. Members, \$60.00; Non-Members, \$120.00
- 7 **GASTRO-ENTEROLOGY**—Graduate Hospital of the University of Pennsylvania, Philadelphia; Dr. Henry L. Bockus, Director—1½ weeks, Nov. 17–26; Fee—A.C.P. Members, \$45.00; Non-Members, \$90.00
- 8 **INTERNAL MEDICINE**—University of Texas School of Medicine, Galveston; Dr. Charles T. Stone, Director—two weeks, Dec. 1–13; Fee—A.C.P. Members, \$60.00; Non-Members, \$120.00
- 9 **MECHANICS OF DISEASE**—Peter Bent Brigham Hospital, Boston; Dr. George W. Thorn, Director—two weeks, dates and fees not yet determined.
- 10 **CHEMOTHERAPY—NEW DRUGS**—Evans Memorial Hospital, Boston; Dr. Chester S. Keefer, Director—one week, dates and fees not yet determined.

At the time of release of this news item (June 18, 1947), the Committee is also considering a course in cardiology at Yale University School of Medicine, New Haven, under the directorship of Dr. H. M. Marvin, and a course in electrocardiography at Emory University School of Medicine, Atlanta, under the direction of Dr. R. Bruce Logue.

A preliminary Postgraduate Bulletin will be published by mid-summer and distributed to all members; however, members of the College desiring to make reservations in any of these courses may do so in advance by communicating directly with

Mr. E. R. Loveland, Executive Secretary  
4200 Pine St.  
Philadelphia 4, Pa.

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#### EXAMINATIONS BY THE AMERICAN BOARD OF INTERNAL MEDICINE

A special oral examination will be held in Chicago October 8, 9 and 10, 1947. The date for closing acceptance of applications will be August 1, 1947.

The next written examination by this Board will be held in various centers over the country on October 20, 1947.

The oral examination is open only to those who have already passed the written portion of the examination. For filing applications or obtaining information, address

Dr. William A. Werrell  
Assistant Secretary-Treasurer  
American Board of Internal Medicine  
1 W. Main St.  
Madison 3, Wis.

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#### MID-WEST REGIONAL MEETING AND POSTGRADUATE COURSE IN INTERNAL MEDICINE

The midwestern states, embracing Illinois, Indiana, Michigan, Minnesota, and Wisconsin, with invited participation by North Dakota, South Dakota, Nebraska, Wyoming, Montana, Iowa, and Kentucky, have determined upon holding their Regional Meeting at the Schroeder Hotel in Milwaukee, on Saturday, November 15,

following a two weeks postgraduate course in Internal Medicine at the University of Wisconsin Medical School, from November 3 to 14.

The postgraduate course will be under the official auspices of the College Committee on Postgraduate Courses, and will be directed by Dr. William S. Middleton. The registration will be limited to 25 members of the College. The course will be concluded by an all day Regional Meeting in Milwaukee. Dr. Karver L. Puestow, A.C.P. Governor for Wisconsin, is the Chairman of the Governors' Committee for the Regional Meeting; Dr. Francis D. Murphy, Milwaukee, is the local general chairman; Dr. Maurice Hardgrove, Milwaukee, is chairman of the Committee on Arrangements and Registration; Dr. Llewellyn R. Cole, who is coördinator of Graduate Medical Education at the Wisconsin Medical School, will be the Treasurer. A great deal of thought and enthusiasm are at work to produce an exceptional meeting. Further details and the program will be published in the near future.

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#### REGIONAL MEETINGS, 1947-48

Regional Meetings to occur during the fall or early winter of 1947 are in process of arrangement. A meeting for members of the College in Western Pennsylvania under the Chairmanship of the Governor for that area, will be held in Pittsburgh on September 10. This meeting will be a part of the postgraduate course in Internal Medicine, which is being given under the direction of the Governor, Dr. Roy R. Snowden, F.A.C.P., at that time. A meeting will be held at Oklahoma City on September 20 under the Chairmanship of Dr. Wann Langston, Governor for Oklahoma, for members of the College in Oklahoma. Members of the College residing in Western Michigan will hold a meeting at Muskegon at a date in October not yet selected. This meeting will be under the Chairmanship of Dr. William M. LeFevre, F.A.C.P. A Regional Meeting for North Carolina is being arranged to take place at Chapel Hill at some date during October or November. Dr. Robert L. McMillan, F.A.C.P., of Winston-Salem, will act as Chairman of the Program Committee. A meeting is planned to take place at Tampa, Fla., on December 8 and 9. Under the Governorship of Dr. Turner Z. Cason, F.A.C.P., and the Chairmanship of Dr. William C. Blake, F.A.C.P., Tampa, this meeting is planned for members of the College in Georgia, Alabama, and South Carolina.

The programs of these meetings and additional details will be published in subsequent issues of the ANNALS.

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#### MISSISSIPPI MEMBERS HOLD REGIONAL MEETING AT BILOXI

The annual luncheon meeting of the Mississippi members of the American College of Physicians was held May 7, 1947, during the Mississippi State Medical Society meetings at Biloxi, Miss. The attendance was good. The guest speaker was Dr. Thomas P. Findley, F.A.C.P., Assistant Professor of Medicine, Tulane University of Louisiana School of Medicine and member of the staff of the Ochsner Clinic, New Orleans, La. Dr. Findley's subject was "Clinical Aspects of Neurohypophyseal Functions."

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#### AMERICAN BOARD OF INTERNAL MEDICINE

The American Board of Internal Medicine has modified its regulations governing the number of written examinations authorized and the interval between written examinations.



Effective January 1, 1946, not more than three written examinations will be authorized. The interval between the first and the second written examinations will be one year. The interval between the second and third written examinations will be two years. A fee of five dollars (\$5.00) is required for each additional written examination.

This ruling does not make it mandatory for a candidate to repeat the examination within one or two years, since each candidate may elect a larger interval. All written examinations are held on the third Monday in February and the third Monday in October of each year.

Not more than three oral examinations are authorized. The interval between the first and second oral examination will be one year. The interval between the second and third oral examination will be two years. A fee of ten dollars (\$10.00) is required for each additional oral examination. Candidates may elect a larger interval if desired. The oral examinations are held regularly each year just in advance of the meetings of the American College of Physicians and the American Medical Association and at such other times and places as the Board may designate.

All candidates must pass the written examinations before admission to the oral is authorized. Oral examination in the sub-specialties recognized by this Board will be given at the time and place of the oral examination in general medicine. All candidates in a sub-specialty must file an application on a form provided for that purpose. All applications must be approved by the Advisory Board concerned and all candidates must have passed the oral examination in internal medicine before admission to the oral in a sub-specialty.

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#### ADVISORY COMMITTEE ON POSTGRADUATE COURSES

When the membership of the Advisory Committee on Postgraduate Courses was published in the May, 1947, issue, two appointments to that Committee had not yet been made. Dr. Walter L. Palmer, Chairman of the Board of Governors, has since appointed, as additional members of this committee, Dr. J. Edwin Wood, Jr., F.A.C.P., Charlottesville, Va., and Dr. Karver L. Puestow, F.A.C.P., both of whom are members of the Board of Governors:

Edward L. Bortz, *Chairman*, Philadelphia, Pa.

Edgar V. Allen, Rochester, Minn.

Turner Z. Cason, Jacksonville, Fla.

Karver L. Puestow, Madison, Wis.

J. Edwin Wood, Jr., Charlottesville, Va.

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#### AMERICAN MEDICAL ASSOCIATION MEETINGS, ATLANTIC CITY, JUNE 9-13

At the very interesting and well-attended Annual Meeting of the American Medical Association, which took place during the week of June 9-13, Dr. Edward L. Bortz, College Governor for Eastern Pennsylvania, was installed as President of the Association. Dr. Roscoe L. Sensenich, F.A.C.P., of South Bend, Ind., who has served as Chairman of the Board of Trustees of the Association, was elected to the position of President-elect. Dr. Sensenich will, therefore, succeed Dr. Bortz as President during the year 1948-49.

The Association decided during the meetings upon the following locations for Annual Meetings during the next three years: 1948, Chicago; 1949, Atlantic City; 1950, San Francisco.

## GIFTS TO THE COLLEGE LIBRARY

Dr. John Mumford Swan, F.A.C.P., Rochester, New York has presented to the library of the American College of Physicians a copy of "Universa Medicina" by Iohannis Fernell II, as published in 1679. As was the custom of the day, the book is printed in Latin, possibly from wood cuts. The book contains approximately nine hundred pages, including a complete index, and is in a very excellent state of preservation.

Dr. James J. Waring, F.A.C.P., Denver, Colo., has presented a copy of the "Rocky Mountain Conference on Infantile Paralysis," published by the University of Colorado School of Medicine and Hospitals.

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REDISTRIBUTION OF TERRITORY TO GOVERNORS FOR EASTERN AND WESTERN  
NEW YORK

On recommendations of Dr. Edward C. Reifenstein, Sr., College Governor for Western New York, and Dr. Asa L. Lincoln, College Governor for Eastern New York, the Board of Regents has re-assigned New York territory as follows: henceforth, Western New York shall include not only all of Western New York, but also Northern New York, down to Albany, and all territory west of a line joining Albany with Binghamton. Eastern New York shall include all territory East or South of the connecting line between Albany and Binghamton. It is felt that this division is more in keeping with the interests of local groups as well as a more appropriate numerical distribution. Members in greater New York and closely adjoining territory probably have less interest and much less contact with members in the State at large.

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Dr. Frederick A. Johansen, Medical Director (R), USPHS, F.A.C.P., has succeeded Dr. Guy H. Faget, USPHS, F.A.C.P., as Medical Officer in charge of the U. S. Marine Hospital, Carville, La.

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The Legion of Merit has been bestowed on Dr. E. Rankin Denny, F.A.C.P., Tulsa, Okla. In the citation reference is made to the studies which Dr. Denny conducted at the Gardiner General Hospital, Chicago, on the action of penicillin. Dr. Denny served in the Army of the United States.

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Members of the College are actively engaged in the work of the Wayne County, Mich., Medical Society. Officers for the year 1947-48 include, as President-elect, Dr. Douglas Donald, F.A.C.P., and College Governor for Michigan; as Trustee, Dr. Edward D. Spalding, F.A.C.P.; as Chairman of the Medical Section, Dr. Robert J. Schneck, F.A.C.P.; and as Secretary of the Medical Section, Dr. Sidney Adler, F.A.C.P. Drs. James J. Lightbody, F.A.C.P., and Ralph A. Johnson (Associate), are serving as Associate Editors of the Detroit Medical News.

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On the occasion of the Annual Luncheon of the California Tuberculosis Association on March 29, 1947, medals were presented to Dr. Frank M. Pottenger, Sr., F.A.C.P., Monrovia, and Dr. George H. Evans, F.A.C.P., San Francisco. The medals recognized the extensive and distinguished contributions of Drs. Pottenger and Evans to our knowledge of the subject of tuberculosis.

Dr. James Morison Faulkner, F.A.C.P., Boston, became Dean of the Boston University School of Medicine on June 1. Dr. Faulkner is a graduate of the Harvard Medical School and a former resident of the Hospital of the Rockefeller Institute and the Johns Hopkins Hospital. Prior to his entry into the Medical Corps, U. S. Naval Reserve, during the recent War, Dr. Faulkner was a member of the faculty of the Boston University School of Medicine, and Physician and Cardiologist in the Massachusetts Memorial Hospitals. In 1946 Dr. Faulkner was appointed Professor of Medicine in the Tufts College Medical School and Director of the first and third Medical Services at the Boston City Hospital.

On June 1 Brigadier General Raymond W. Bliss succeeded Major General Norman T. Kirk, F.A.C.P., as Surgeon General of the United States Army, for a term of four years. Dr. Bliss, who entered the Army in 1911, graduated from the Tufts College Medical School in 1910. He subsequently attended the Army Medical School and received special training in Surgery at Harvard. From January, 1946, until this June he was Deputy Surgeon General.

#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to June 17, 1947 inclusive).

Arden Freer, Neversink, N. Y. (Col., MC, USA)  
 Samuel Edward King, New York, N. Y. (Lt. Col. MC, AUS)  
 H. Beckett Lang, Albany, N. Y. (Comdr., MC, USNR)  
 Richard M. McKean, Detroit, Mich. (Col., MC, AUS)  
 Jerome T. Paul, Chicago, Ill. (Major, MC, AUS)  
 Nathaniel E. Reich, Brooklyn, N. Y. (Major, MC, AUS)  
 Donald S. Smith, Pontiac, Mich. (Lt. Comdr., MC, USN)

#### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948 to June 30, 1949. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from \$2,200 to \$3,000.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

## ABRIDGED MINUTES, BOARD OF REGENTS

## FIRST MEETING

CHICAGO, ILL.

APRIL 27, 1947

The first meeting of the Board of Regents during the 28th Annual Session of the American College of Physicians convened at 2:00 p.m., April 27, 1947, at the Palmer House, Chicago, President David P. Barr presiding, with Mr. E. R. Loveland acting as Secretary and with the following in attendance:

David P. Barr	<i>President</i>
Hugh J. Morgan	<i>President-Elect</i>
James J. Waring	<i>1st Vice President</i>
A. B. Brower	<i>2nd Vice President</i>
T. Homer Coffen	<i>3rd Vice President</i>
William D. Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary General</i>
Maurice C. Pincoffs	<i>Editor</i>
Chauncey W. Dowden	<i>Chairman, Board of Governors</i>
Francis G. Blake	
James F. Churchill	
Reginald Fitz	
Roger I. Lee	
Charles T. Stone	
Walter B. Martin	
William S. Middleton	
James E. Paullin	
LeRoy H. Sloan	
George F. Strong	
Ernest E. Irons	
William S. McCann	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	

Abstracted minutes of the previous meeting of the Board were read by the Secretary and by resolution approved as read.

President Barr invited Mr. Royal Ryan of the New York Convention Bureau to present an invitation from New York City for the College to meet there in 1948. After presenting an invitation on behalf of the civic bodies, the County Medical Society, and the New York Academy of Medicine, and describing New York's facilities, Mr. Ryan answered numerous questions and retired. It was explained that the meeting city for 1948 would be selected by the new Board of Regents at its meeting on Friday, May 2.

President Barr requested Dr. Hugh J. Morgan to present a Memorial to the late Dr. James D. Bruce in accordance with directions of the Board of Regents at its previous meeting, whereupon Dr. Morgan read the following Memorial which was approved, spread upon the minutes, and a copy authorized to be sent to Mrs. Bruce:

"IN MEMORIAM  
JAMES DEACON BRUCE  
1872-1946

"James Deacon Bruce, a Fellow of the American College of Physicians since 1925, died at Ann Arbor, Michigan, September 5, 1946. He served as Governor, Regent and President of the College. His many and notable contributions to medical education and medical statesmanship in this country have been reviewed and evaluated by Dr. H. H. Riecker in the *ANNALS OF INTERNAL MEDICINE*.

"As a member of this Board of Regents and a patron of the College, he was outstanding; but, we, of the Board, do not cherish his memory for this reason alone, nor was it for this reason alone when he was with us that we most appreciated him.

"He was cultured and not merely learned; he used his wit for merriment and not malice; he was candid without tactlessness, and friendly without affectation. In the Board of Regents, his companionship was a privilege and a joy to all. Whether in the rôle of presiding officer or participant in debate, his humor, charm and courtesy were as unfailing as his wisdom and idealism. His discussions of matters under consideration by the Board were marked by simplicity, dignity and forcefulness and they revealed the high ideals and purposes of his life.

"This small tribute, all the more because it is the expression of our sincere sorrow, must fall short of doing justice either to the sentiments of the members of the Board of Regents or to the worth of our friend. We mourn his passing; we are grateful for our association with him, and we shall remember him always with affection and pride."

At direction of the President, the Secretary, Mr. Loveland, presented the following communications:

- (1) Notification from Dr. James J. Waring of his resignation from the American Board of Internal Medicine on June 30, 1947, with a memorandum of the fact that his unexpired term is two years, or until June 30, 1949.
- (2) Notification from the American Board of Internal Medicine that the terms of Drs. Cecil J. Watson, William S. McCann, and William B. Porter, appointees of the American College of Physicians on the Board, will expire July 1, 1947, with a notation that all three are eligible for re-appointment.
- (3) An announcement that Dr. Robert B. Radl, Bismarck, had been appointed, by the President, Interim Governor for North Dakota, to act until the next regular election, due to the death of Dr. Julius O. Arnson, Governor for that state. The By-Laws provide that the President shall make interim appointments until the next regular election.
- (4) A report that President Barr had appointed Dr. William Gerry Morgan, M.A.C.P., representative of the College at the annual meeting of the Gorgas Memorial Institute of Tropical Medicine.
- (5) An announcement that President Barr had appointed Dr. Harry Plummer Ross, F.A.C.P., to represent the College at the inauguration of Thomas Elsa Jones, seventh President of Earlham College.
- (6) Announcement that President Barr had appointed Dr. Francisco de P. Miranda, F.A.C.P., College Governor for Mexico, as official representative of the College at the inaugural ceremonies of the Hospital de Enfermedades de la Nutricion.
- (7) An announcement that President Barr had appointed Dr. Walter Freeman, F.A.C.P., representative of the College in the Division of Medical Sciences

of the National Research Council, for a three-year term from July 1, 1947, to succeed Dr. Wallace M. Yater whose term will have expired at that time.

- (8) An announcement that President Barr had appointed Dr. George Morris Piersol, F.A.C.P., and Dr. Edward L. Bortz, F.A.C.P., as representatives of the College to a recent UNESCO meeting at Philadelphia, March 24-26, 1947.
- (9) A communication from Science Service proposing to issue privilege cards to members of the American College of Physicians, entitling each to a special subscription rate to the "Science News Letter."

(Upon motion regularly made and seconded, it was voted not to take advantage of this offer by Science Service.)

- (10) A recommendation from the Marshal, Dr. T. Grier Miller, that the names of newly elected Fellows be not formally read at the Convocation, but that their names be included in a published roster which shall be handed by the Chairman of the Committee on Credentials to the President during the induction ceremonies.

(It was moved by Dr. Paullin and seconded by Dr. Brower that the recommendation of the Marshal be approved. There followed a discussion in which Dr. Fitz pointed out that a survey had been made some years ago which resulted in an indication that the reading of the names of new Fellows is a procedure well worth carrying forward. This survey had been made among the younger and newer Fellows of the College who felt the reading of the names a minimal recognition. The motion was put to vote and adopted with 17 voting in favor and 6 against.)

- (11) A letter of appreciation from Dr. David D. Rutstein, Medical Director of the American Council on Rheumatic Fever, acknowledging receipt of the gift of \$1,000.00 by the American College of Physicians toward the work of that Council.
- (12) A letter of acknowledgment and appreciation from the Secretary of the University of Chicago, Board of Trustees, for a donation of \$1,730.87, proceeds from a postgraduate course directed by Dr. Walter L. Palmer for the American College of Physicians, the donation being in support of a Fellowship in gastro-enterology at that institution.
- (13) A report from Dr. George C. Griffith, F.A.C.P., Director of one of the College courses in cardiology during the spring of the current year, in which Dr. Griffith reported a surplus of somewhat over \$500.00, which had been turned over to the College Governor for Southern California, Dr. Leland Hawkins, for use by the College for postgraduate activities in that region.
- (14) A letter from Dr. Edgar V. Allen, F.A.C.P., Director of a recent course in peripheral vascular disease at the Mayo Foundation, under the auspices of the College, requesting approval by the College to turn over a surplus of \$453.46 from the course to the George Brown Memorial Lectureship Fund. Faculty members on the course are not permitted to receive fees for their services and Dr. Allen, therefore, recommended this manner of disposing of the balance, especially in view of the fact that the fund had been substantially depleted.

(It was moved by Dr. Lee and seconded by Dr. Fitz that the fund be expended as suggested in Dr. Allen's letter. There was a general discussion in which the thought was expressed that funds contributed for postgraduate courses offered by the

College ought not to be spent for any other than strictly College purposes. It was, however, pointed out that all tuition fees collected by the College heretofore are turned over to the Director of the course for use by him or his institution in whatever manner he may select. In some instances such funds have been used for Fellowships, for additions to the library fund of the school, and, in other instances, have been distributed pro rata to the faculty. Dr. Churchill advocated that the College establish a definite policy for the future. President Barr advised against specifying exactly how these funds shall be used, because custom might vary greatly in different places and it might be embarrassing to have to conform to a very specific rule. The motion was put to vote and carried.)

- (15) A letter addressed to the Board of Regents from Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., concerning the American Board of Internal Medicine, with special reference to the abolition of preceptorships and the new type of "multiple choice" examinations initiated during October, 1946. Dr. Yater suggested that the American College of Physicians and the Section on Medicine of the American Medical Association have a greater part than at present in determining the policies of the Board.

President Barr questioned whether the letter was in such form as could be submitted to action by the Board of Regents at the time and he called upon Dr. Waring, Chairman of the American Board of Internal Medicine, for comments.

Dr. Waring expressed with great sincerity and conviction his explicit confidence in the American Board as it was constituted in the past and as it is now constituted. He commended the earnest, hard-working, thoughtful group of men who are members of the Board. He stated that the preceptorship plan had been a sad failure but gave assurances that the Board, after careful study, was prepared to offer a substitute for the preceptorship plan which will satisfy all critics of the Board. In regard to the new type of examination, he pointed out the utter impossibility of individually grading the essay type of examination for the ever growing number of candidates for certification. He said also that it is common knowledge that many of the departments of education in some of our best universities feel that the essay type of examination is a poor medium to explore the depths and the efficiency of a man's knowledge in any particular subject. Dr. Waring said further that the Board had been fortunate in having among its members at least three men who had had much experience with the new type of multiple choice examinations, and that from their experience, the Board will refine, improve and perfect the new type of examination suitable to this particular organization. He admitted that the mortality in the October, 1946, examination had been high, partly due to insufficient experience in submitting the new type of examination and partly due to the fact that the Board had set its standards a little high on that particular occasion.

Dr. Irons said the Board of Internal Medicine needs no defense. He discussed, at some length, the matter of preceptorships and the new multiple choice type of examination. He emphasized that on all occasions the Board of Internal Medicine has taken great care to avoid unfairness. He recommended that the American Board of Internal Medicine should not be dominated by the American College of Physicians or the Section on Internal Medicine of the American Medical Association, but should remain autonomous—loss of autonomy would introduce, in Dr. Irons' opinion, a number of elements of danger.

Dr. McCann, a member of the Board of Internal Medicine, explained at some length the basic principles and objectives and operation of the multiple choice type of examinations, adding, "I think that there is one valuable thing that comes from this method of examination and that is the questions themselves can be assessed. After our first effort, we heard grumbling because some questions appeared to have two or three correct answers, and, of course, they were keyed for just one. The questions

have been subjected to analysis in this way: If the candidates are divided into three groups, the high group, the middle group, and the low group, and the percentage of men getting the keyed answer in each group is compared, a good question is one which will have a high percentage of correct answers in the top group, a lesser percentage in the middle group and a small percentage in the lower group. A question that gives fairly uniform results throughout the three groups is not a good question; it is too easy. A question that has a low score in the high group is either wrong or too hard—probably it is a wrong question. These problems are being studied in that way and as examinations go on and experience accumulates, the examinations will be better."

(A motion to refer Dr. Yater's letter to the American Board of Internal Medicine had been made by Dr. Lee, seconded by Dr. Stroud, and following the above discussion, was adopted.)

#### Communications Continued:

- (16) A letter from Dr. E. J. Kepler, submitted through Dr. Edgar V. Allen, inquiring about the possibilities of conferring an honorary Fellowship upon an eminent Buenos Aires internist. Dr. Kepler had been informed that the By-Laws of the College do not provide in any manner for honorary Fellowships.
- (17) A letter from Dr. Nelson G. Russell, suggesting that the College should have a hood representing the organization for use of its representatives at academic functions. The Board was reminded that this matter was carefully studied several years ago with the result that the College adopted an official Fellowship Chevron to be worn on the academic gown on such occasions.
- (18) An inquiry from Dr. Karl Rothschild, F.A.C.P., regarding eligibility of candidates holding honorary medical degrees. The Secretary pointed out that the By-Laws provide, "A candidate shall be a graduate of an approved medical school."

(After some discussion, it was moved by Dr. Piersol, seconded by Dr. Brower, and carried, that honorary medical degrees cannot be recognized in the College as the equivalent of a Degree of Medicine.)

#### *New Business*

The Secretary reported that in accordance with the By-Laws of the College, one Fellow had been dropped from the Roster as of the current day because of delinquency in dues of two years or more. It was pointed out that this is a most unusual record to have but one member dropped for delinquency out of the entire membership.

Report of the Secretary General, Dr. George Morris Piersol: "Deaths since the last meeting of this Board include 32 Fellows and 4 Associates as follows:

#### *"Fellows"*

Arnson, Julius O.	Bismarck, N. D.	October 29, 1946
Barbash, Samuel	Atlantic City, N. J.	November 14, 1946
Beling, Christopher Charles	Newark, N. J.	November 30, 1946
Benoit, Emmanuel P.	Montreal, Que., Can.	April 14, 1946
Briskman, A. Lee	Denver, Colo.	November 26, 1946
Brown, Mark A.	Cincinnati, Ohio	January 13, 1947
Chapman, George A.	Glens Falls, N. Y.	December 16, 1946
Deaderick, William H.	Hot Springs National Park, Ark.	March 11, 1945



Eschweiler, Paul C.	Little Rock, Ark.	August 23, 1946
Favill, John	Chicago, Ill.	December 21, 1946
Fish, Clyde Mulhollon	Pleasantville, N. J.	November 21, 1946
Flynn, James Murray	Rochester, N. Y.	December 14, 1946
Gaumer, James Stewart	Fairfield, Iowa	September 9, 1946
Hardisty, Richard H. M.	Montreal, Que., Can.	November 12, 1946
Held, Isidore William	New York, N. Y.	March 2, 1947
Hill, Harold Phillips	San Francisco, Calif.	December 3, 1946
Johnson, Trimble	Atlanta, Ga.	October 6, 1946
McBride, Robert E.	Las Cruces, N. M.	January 17, 1947
McCain, Paul Pressly	Sanatorium, N. C.	November 25, 1946
Mount, Frank R.	Portland, Ore.	October 11, 1946
O'Mara, John T.	Baltimore, Md.	March 3, 1946
Preston, John William	Roanoke, Va.	January 1, 1947
Rosenfeld, Joseph	Youngstown, Ohio	November 4, 1946
Roses Artau, Miguel	San Juan, P. R.	July 17, 1945
Roth, Paul	Battle Creek, Mich.	November 6, 1946
Sargent, Ara N.	Salem, Mass.	August 26, 1946
Schleiter, Howard G.	Pittsburgh, Pa.	February 5, 1947
Shearer, Thomas Laidlaw	Baltimore, Md.	December 13, 1946
Todd, Lucius Newton	Augusta, Ga.	December 12, 1946
Topmoeller, George B.	Cincinnati, Ohio	October 3, 1946
Van Valzah, Robert	Goby, Va.	November 23, 1946
Wilson, Frank Wiley	M.C., U. S. Army	April 20, 1946

### "Associates

Nelson, Parley	Idaho	September 12, 1946
Rosenblum, Alex Morton	Rexburg, Idaho	September 6, 1946
Stoneburner, Lewis T., III	Youngstown, Ohio	November 10, 1944
Waud, Sydney Peyster	Richmond, Va.	October 19, 1946
	Chicago, Ill.	

"There may be other deaths that have not yet been reported.

"There are 119 new and additional life members, bringing the grand total to 612 of whom 46 are deceased, leaving a balance of 566. The names of the new life members are as follows (listed in order of subscription):

"Henry Monroe Moses	Brooklyn, N. Y.
Henry Weyler	Providence, R. I.
William E. G. Lancaster	Fargo, N. D.
Andrew Blair	Charlotte, N. C.
Paul F. Liva	Lyndhurst, N. J.
J. K. Williams Wood	Troy, Pa.
C. DeWitt Briscoe	Panama, R. P.
Carol C. Turner	Memphis, Tenn.
John Russell Twiss	New York, N. Y.
William R. Blue	Memphis, Tenn.
William M. Sheppe	Wheeling, W. Va.
Hildegard G. Sinnock	Quincy, Ill.
George L. Steele	Springfield, Mass.
John I. Marker	Davenport, Iowa
Lorenzo D. Massey	Osceola, Ark.
Felix R. Park	Tulsa, Okla.
Samuel Goodman	Tulsa, Okla.
E. Cooper Cole	Toronto, Ont., Canada

Murray DeArmond  
Joseph F. Hamilton  
W. LeRoy Dunn  
Harold K. Eynon  
Evert A. Bancker  
Hugh E. Kiene  
Isidore Lattman  
Lemuel C. McGee  
Matthew Molitch  
Glenn Edward Drewyer  
Carl H. Fortune  
Frank F. D. Reckord  
Charles Windwer  
Samuel C. Arnett, Jr.  
Frank C. Clifford  
Charles W. McClure  
Ernest G. McEwen  
John B. D'Albora  
Richard F. Herndon  
Mary McIndoe Spears  
William Stein  
Kenneth Taylor  
Clarence L. Andrews  
John V. Barrow  
Roland Cummings  
Frederick K. Herpel  
Donald L. Kegaries  
Clyde H. Kelchner  
Elmer A. Kleefield  
Robert C. Levy  
Samuel A. Munford  
Joseph Maxime Perret  
E. Clarence Rice  
Horace R. Livengood  
Gordon Botkin Wilder  
Cleo Russel Gatley  
Roy S. Leadingham  
George T. Strodl  
Leslie R. Webb  
Otto G. Wiedman  
Gordon R. Kamman  
Frank B. Queen  
F. Eugene Zemp  
Edwin F. Hirsch  
O. B. Kiel  
Albert H. Rowe  
Madelaine R. Brown  
Hubert M. Parker  
Harry Ernest Flansburg  
James E. Hunter  
Wingate M. Johnson  
Flavius Downs Mohle

Indianapolis, Ind.  
Memphis, Tenn.  
Washington, D. C.  
Collingswood, N. J.  
Atlanta, Ga.  
Providence, R. I.  
Washington, D. C.  
Wilmington, Del.  
Atlantic City, N. J.  
Glenwood Springs, Colo.  
Lexington, Ky.  
Harrisburg, Pa.  
Brooklyn, N. Y.  
Lubbock, Tex.  
Toledo, Ohio  
Boston, Mass.  
Evanston, Ill.  
Brooklyn, N. Y.  
Springfield, Ill.  
Philadelphia, Pa.  
New Brunswick, N. J.  
New York, N. Y.  
Atlantic City, N. J.  
Los Angeles, Calif.  
Los Angeles, Calif.  
West Palm Beach, Fla.  
Rapid City, S. D.  
Allentown, Pa.  
Forest Hills, N. Y.  
Chicago, Ill.  
Clifton Springs, N. Y.  
New Orleans, La.  
Washington, D. C.  
Elizabeth, N. J.  
Anderson, Ind.  
Pontiac, Mich.  
Atlanta, Ga.  
New York, N. Y.  
Springfield, Mo.  
Hartford, Conn.  
St. Paul, Minn.  
Portland, Ore.  
Columbia, S. C.  
Chicago, Ill.  
Wichita Falls, Tex.  
Oakland, Calif.  
Boston, Mass.  
Kansas City, Mo.  
Lincoln, Nebr.  
Seattle, Wash.  
Winston-Salem, N. C.  
Houston, Tex.

Clarence W. Olsen  
 Cecil L. Rudesill  
 Jacob Schwartz  
 Joseph Kaufmann  
 James Thomas Gilbert, Jr.  
 Edward Urbane Reed  
 Paul J. Breslich  
 B. Smith Hopkins, Jr.  
 Albert A. Hornor  
 Kenneth Kyler Sherwood  
 Theodore F. Bach  
 Harold I. Kinsey  
 Edward C. Reifenstein, Sr.  
 Rufus S. Reeves  
 H. Milton Rogers  
 Joseph Weinstein  
 James Clyde Waddell  
 Maurice Anthony Donovan  
 Thomas Balfour Dunn  
 Charles E. Leonard  
 Pablo Morales-Otero  
 Robert P. Wallace  
 William W. Fox  
 Carl O. Rinder  
 Amadeo Vicente-Mastellari  
 Carl A. Hartung  
 William C. Menninger  
 Robert S. Dow  
 Arthur Lee Osterman  
 Everett E. Hammonds  
 Henry Clay Long  
 Delbert H. McNamara  
 Aldis A. Johnson  
 George O. Solem  
 Edward C. Koenig  
 James Steele  
 James R. Gudger  
 John Noll, Jr.  
 Henry Allen Tadgell  
 Harry L. Huber  
 George F. Lull  
 Robert Henry Southcombe  
 Richard Francis McLaughlin  
 Dwight Locke Wilbur  
 Henry Cook Macatee  
 Abraham S. Rubnitz  
 William Miller Dugan  
 Abraham Klein  
 Saul Solomon

Beverly Hills, Calif.  
 Indianapolis, Ind.  
 Brooklyn, N. Y.  
 Montreal, Que., Canada  
 Bowling Green, Ky.  
 Los Angeles, Calif.  
 Minot, N. D.  
 Urbana, Ill.  
 Boston, Mass.  
 Seattle, Wash.  
 Philadelphia, Pa.  
 Toronto, Ont., Canada  
 Syracuse, N. Y.  
 Philadelphia, Pa.  
 St. Petersburg, Fla.  
 Brooklyn, N. Y.  
 Beatrice, Nebr.  
 Schenectady, N. Y.  
 Oakland, Calif.  
 Oklahoma City, Okla.  
 Santurce, P. R.  
 New York, N. Y.  
 Atlantic City, N. J.  
 Chicago, Ill.  
 Panama, R. P.  
 Chattanooga, Tenn.  
 Topeka, Kans.  
 Portland, Ore.  
 Wheeling, W. Va.  
 Birmingham, Mich.  
 Knoxville, Tenn.  
 Santa Barbara, Calif.  
 Council Bluffs, Iowa  
 Chicago, Ill.  
 Buffalo, N. Y.  
 Brooklyn, N. Y.  
 New York, N. Y.  
 Youngstown, Ohio  
 Belchertown, Mass.  
 Chicago, Ill.  
 Chicago, Ill.  
 Spokane, Wash.  
 Burlingame, Calif.  
 San Francisco, Calif.  
 Washington, D. C.  
 Omaha, Nebr.  
 Indianapolis, Ind.  
 Brooklyn, N. Y.  
 New York, N. Y."

It was pointed out that more life members have been added during the preceding twelve months than for any other like period in the history of the College.  
 (The report of the Secretary General was accepted by resolution.)

Report of the Committee to Study the Bruce Memorial Medal, Dr. George Morris Piersol reporting in the place of the Chairman, Dr. O. H. Perry Pepper: "Dr. Pepper and I, who constitute this Committee, held several meetings and arrived at the following recommendations: It is our well considered opinion that the present medal used by the College for the Phillips Memorial Award should also be used for the James D. Bruce Memorial Medal, appropriately changing the name and the inscription to meet the altered situations. It seems unnecessarily expensive and time consuming to have a new medal designed. As a general principle, we see no reason why the College cannot use the same medal for all awards, changing the inscription each time."

(On motion by Dr. Stroud, seconded by Dr. Morgan, and carried, the above report was approved.)

Report, Committee on Credentials, Dr. George Morris Piersol, Chairman: "The Committee on Credentials held a two-day meeting at the Philadelphia Headquarters on March 29-30, and a meeting at Chicago on the morning of April 27. At the March meeting there were a number of communications:

- "(a) At the instance of Dr. C. F. Moffatt, Regent, Montreal, the Committee considered Fellowship in the Royal College of Physicians and Surgeons of Canada, of England and of Edinburgh. Already with the approval of the Board of Regents, the Committee recognizes certification by the Royal College of Physicians and Surgeons of Canada as acceptable in lieu of certification by the American Board of Internal Medicine. The Committee has reviewed the requirements for Fellowship in the Royal Colleges of England and Edinburgh, through Dr. Moffatt, and now wishes to recommend to the Board of Regents that Fellowship in any of the above Colleges may be accepted in lieu of certification by the Royal College of Physicians and Surgeons of Canada or the American Board of Internal Medicine."

DR. MOFFATT: When I communicated with Mr. Loveland, it was with the understanding then that the F.R.C.P., London and Edinburgh, were acceptable to the Royal College of Physicians and Surgeons of Canada. I now find that the Royal College of Physicians and Surgeons of Canada has raised its standards so that it will not now automatically accept F.R.C.P., London and Edinburgh. It feels that its standards are as high as any other body and it will not automatically accept these two other degrees.

PRESIDENT BARR: In the enlightenment of this statement by Dr. Moffatt, the Credentials Committee may wish to reconsider this matter before presenting it as a recommendation.

DR. PIERSOL: We withdraw this recommendation in lieu of the information that was not previously available.

Continuing the Report:

- "(b) A communication was received concerning the status of the specialty of Physical Medicine. The Chairman pointed out that time will clarify this situation because a separate board of certification in Physical Medicine is now being organized.
- "(c) The Committee reviewed the case of Dr. William D. Mackay (Associate) of Salisbury, Conn., who was elected on April 19, 1942, and a few months thereafter had to retire from practice due to illness. For the entire intervening period he has been ill and living on a farm, unable to make any medical progress whatsoever, or to become certified. Now, at the end of his Associate term, he has largely regained his health and expects in the next few months to return to the practice of medicine on a limited scale in New York City. The Committee appreciates that the strict interpretation of the regulations limiting Associateship to a maximum of five years

visited an unfair hardship upon this candidate, and that on occasion there might be one or more other candidates likewise unfortunate. The Committee recommends to the Board of Regents that they amend the By-Laws that in the case of Associates who have prolonged illnesses during which time they can neither study nor work, that that-time be eliminated from the five-year term and time be extended; also that Dr. Mackay benefit thereby, as provided.

"The Committee realizes that this requires a change in the By-Laws. It is eager to do everything it can for Dr. Mackay but sees no way to extend his term until the By-Laws are changed.

"Application for reinstatement: The Committee recommends to the Board of Regents the reinstatement to Fellowship of Dr. Konrad Birkhaug, Albany, N. Y."

(On motion by Dr. Pincoffs, seconded by Dr. Morgan, and regularly carried, Dr. Konrad Birkhaug was reinstated to Fellowship.)

Continuing Report of Committee on Credentials:

"New Business—

"(a) The Board of Regents on October 20, 1946, adopted a resolution directing that the Credentials Committee review the routine of using the inquiry card system on candidates for Fellowship and Associateship and report back to the Regents. In reviewing the By-Laws of the College, Article V, Section 2, provide, in part, 'further, the name of the candidate (for Fellowship) shall be sent to each Fellow in the candidate's locality, with a request for comments as to the candidate's fitness.' The By-Laws make no such stipulation with regard to the candidates for Associateship, although it has been the custom to use the inquiry cards for Fellow and Associate candidates alike.

"The College membership has grown so great that the card system has become top heavy, requiring, in some instances, up to three hundred cards for a single candidate with consequent great expenditure of labor, materials and postage, and with the growing number of cards it becomes the more difficult and time-consuming to pass on the credentials of each candidate. The Committee considered several possible substitutes, and is now ready to recommend to the Board of Regents the discontinuance of the individual inquiry card system, and to substitute in its place the publication of a printed list of all candidates, to be distributed to Fellows and Masters of the College adequately in advance of each Credentials Committee meeting, thus giving every Fellow or Master an opportunity to vote for or against any candidate. The Committee further recommends that all proposals shall be required to be filed sixty days in advance of the Committee meeting, thus giving the Executive Offices adequate time to publish and distribute the lists and to receive the votes.

"This recommendation, in the opinion of the Credentials Committee, will be more effective and more economical, and will not require any change in the present By-Laws, in view of the fact that the By-Laws do not specify in what manner the names of candidates shall be submitted to the Fellows and Masters of the College."

In discussing this matter Dr. Piersol pointed out that this published list will go to all Fellows of the College in one general mailing and that the names will be arranged geographically for easy reference. It will be required that each proposal be filed at least 60 days before the meeting of the Credentials Committee; the published list will

be mailed during the 60-day interim. No names will be included on the list unless the proposal is filed with the Executive Offices as specified. This will eliminate the last-minute going over of certain additional names, which happens every year, and which is most unsatisfactory and probably unnecessary. It is due largely to oversight on the part of sponsors and, in some instances, to lack of attention of the Governor. This recommendation has been the result of much discussion and is the only solution we have to recommend, he said.

(On motion by Dr. Brower, seconded by Dr. Irons, and regularly carried, this recommendation of the Committee was approved.)

Dr. Piersol, continuing the Report of the Credentials Committee:

“(b) Candidates for Fellowship: The following is a summary of the recommendations of the Committee (a list of the recommended candidates for Fellowship has been placed in the hands of all Regents and Governors):

“Recommended for Advancement to Fellowship . . . .	102	
Recommended for Direct Election to Fellowship . .	22	124
Recommended for Election first to Associateship . . . . .		6
Deferred . . . . .		42
Rejected . . . . .		10
		<hr/>
		182

“It is recorded of the 22 candidates recommended for election directly to Fellowship, 4 were former Associates who previously were dropped for failure to qualify but were given credit for their Associate terms, and who now have presented adequate and satisfactory credentials for Fellowship.

“The Committee recommends to the Board of Regents the election to Fellowship of the 124 candidates on this list.” (This list of 124 candidates has been combined with the list recommended for election at the meeting on April 27, 1947, and has been published in the May, 1947, issue of this journal.)

(On motion by Dr. Piersol, seconded, and regularly carried, the candidates (124) on the list were formally elected to Fellowship.)

Dr. Piersol, continuing the Report:

“(c) Candidates for Associateship: The following is a summary of the recommendations of the Committee (a list of the recommended candidates for Associateship has been placed in the hands of all Regents and Governors):

“Recommended for Election to Associateship . . . . .	194	
*Fellowship Candidates Recommended for Election		
First to Associateship . . . . .	6	200
Deferred . . . . .		44
Rejected . . . . .		25
		<hr/>
		263
	* plus	6

“The Committee recommends to the Board of Regents the election to Associateship of the 200 candidates on this list.” (This list of 200 candidates has been combined with the list recommended for election at the meeting on April 27, 1947, and has been published in the May, 1947, issue of this journal.)

(On motion by Dr. Morgan, seconded by Dr. Tenney, and regularly carried, the group of 200 candidates was elected to Associateship.)

Dr. Piersol, continuing his Report:

"The Committee on Credentials again met this morning, with all members present, and considered an additional list of candidates. The meeting ended only a few minutes before the meeting of the Board of Regents began and, therefore, there has been no opportunity to type the prepared list, so we shall have to read the names to you.

"The following is a summary of candidates for Fellowship:

Recommended for Advancement to Fellowship .....	25	
Recommended for Direct Election to Fellowship ....	9	34
*Recommended for Election First to Associateship .....		4
Deferred .....		23
Rejected .....		3
		<hr/>
		64

"The Committee recommends the election of the following 34 candidates to Fellowship." (Reads the list, which has been combined in these Minutes with the list of Fellows previously elected and published in the May, 1947, issue of this journal.)

(On motion by Dr. Lee, seconded by Dr. Morgan, and carried, the 34 candidates were formally elected to Fellowship.)

Dr. Piersol, continuing his Report:

"Candidates for Associateship: The following is a summary of the recommendations of the Committee:

Recommended for Election to Associateship .....	66	
*Fellowship Candidates Recommended for Election		
First to Associateship .....	4	70
Deferred .....		18
Rejected .....		10
		<hr/>
		94
		* plus 4

"The Committee on Credentials recommends to the Board of Regents the election of the 70 candidates to Associateship." (Reads the list of names, which have been combined with the list of Associates previously elected at this meeting and published in the May, 1947, issue of this journal.)

(On motion by Dr. Paullin, regularly seconded, and carried, the 70 candidates were formally elected to Associateship.)

Dr. Piersol left the meeting and on request of President Barr, Dr. Sloan continued the report:

"The Committee, after due deliberation, recommends to the Board of Regents election to Mastership in the College of the following:

Dr. Ernest B. Bradley	Lexington, Ky.
Dr. Sydney R. Miller	Baltimore, Md.
Dr. John H. Musser	New Orleans, La.
Dr. George Morris Piersol	Philadelphia, Pa.

"They are all past Presidents of the College, former members of the Credentials Committee, and men who have performed signal service for the College over many years. Dr. Bradley, Dr. Miller and Dr. Musser are incapacitated and are unable to accept their Masterships in person. How-

ever, in their absence, Dr. Ernest E. Irons will act for Dr. Bradley; Dr. William S. Middleton for Dr. Musser; and Dr. Wetherbee Fort for Dr. Miller."

(On motion by Dr. Paullin, seconded by Dr. Stroud, and regularly carried, the above four physicians were elected to Mastership and the recommendation of the Committee on Credentials approved.)

Dr. Roger Lee, Chairman of the Committee on Public Relations, presented a report dealing with numerous communications, resignations and some fees and dues cases. Several of the communications were in regard to possible action by the College in inspecting hospitals and matters of that sort. The general action of the Committee was to report that the American College of Surgeons, whose hospital experts inspect hospitals, and the American Medical Association, through its Council on Medical Education and Hospitals, are at present the official agencies to inspect hospitals for internships and residencies, and to report that The American College of Physicians does not engage in this activity, other than to participate informally with the Council on Medical Education and Hospitals.

On recommendation of the Committee on Public Relations, the resignation of Dr. Robert E. Lyons, Jr. (Associate), Bloomington, Indiana, was accepted. Likewise, in accordance with the recommendations of the Committee, the dues of nine members who are ill and at least temporarily out of practice were waived for the current year and until recovery and resumption of practice.

Report, House Committee, Dr. William D. Stroud, Chairman: "A special meeting of the House Committee was held at the College Headquarters, Philadelphia, on Friday, April 18, with all members present—Dr. Charles L. Brown, Dr. T. Grier Miller, and Dr. William D. Stroud, Chairman.

"In accordance with directions and approval of the Board of Regents at its last meeting, October 20, 1946, the following improvements, within the appropriations, have been completed, inspected and approved by the Committee:

- "(1) a kitchen has been installed on the third floor for the use of the caretakers, and the former basement kitchen has been converted into a machine room for the Addressograph Department;
- "(2) doors, perfectly matching in design the original doors in the building, were installed on the second floor between the Assistant Executive Secretary's general office and private office;
- "(3) four rooms on the upper floors have been renovated and repapered.

"At the last meeting of the Board of Regents, the House Committee was instructed to determine the cost of preparing drawings and specifications for the proposed new addition to the College Building and to further explore the possibilities and cost of building. The Committee has consulted two different architects, including the Trumbauer firm, who were the original architects and building supervisors of the College Headquarters. That firm obviously is thoroughly familiar with every detail of the present building, and one of its officers, Mr. Frank, without obligation to the College and without charge, prepared floor plans and an elevation drawing of the building as it would appear with the proposed extension, said plans and drawings being in my hands for display.

"The Trumbauer firm will prepare plans, specifications, detailed drawings and supervision for the proposed addition for a fee of 6% of the total cost of the work, payments to the architect to be as follows:

- "(1) upon completion of the preliminary studies, one-fifth of the total architect's fee would be payable:



- "(2) upon completion of specifications and general working drawings, two-thirds of the architect's fee will be payable;
- "(3) the balance is payable from time to time during execution of the work, and in proportion to the amount of services rendered by the architect.

"The Trumbauer firm states that the cubical content of the new addition is 39,000 cubic feet, and the approximate cost would be \$48,000.00 (Incidentally, they told us the name of the builder of the present property between 1904 and 1905, at which time the cost was \$50,627.61.)

"The Trumbauer firm furthermore states that in their opinion all materials needed for the addition are readily available, that they feel that building costs of this character are more or less stabilized and would cost no more during the coming year than if delayed for a longer time, say of two years. The only item not available at the present, nor in the future, are bricks of the same length as used in the old building. These no longer are made, but bricks of the same color and thickness are still made, and it is for this reason, the different length of the bricks, that the Trumbauer firm designs the addition with a backset of some eleven feet, which would eliminate any noticeable change in appearance. Furthermore, the Committee, on inspection, believes the designed addition more appropriate for many reasons, than a straight extension of the present building, and points out that the design is in keeping with present architectural policies.

"The other architect consulted quoted a fee of 10% of the total cost of the addition, and estimated its cost at \$80,000.00. The Committee is inclined to believe that the Trumbauer firm, from its own first-hand experience with designing and supervising the construction of the original building, is in a far better position to estimate the cost of the proposed addition. Obviously, there is a wide difference between the two architects' fees—one based on 6% of \$48,000.00, or \$2,880.00, and the other based on 10% of \$80,000.00, or \$8,000.00.

"The Committee unanimously voted to recommend to the Board of Regents at this meeting the approval of the preliminary plans submitted by the Trumbauer firm; the official employment of the Trumbauer firm; the authorization of the Committee to request the Trumbauer firm to obtain two bona fide builders' quotations; and such other authorization to the House Committee and the Executive Committee to proceed in accordance with action taken at this meeting by the Board of Regents."

(On motion by Dr. Irons, seconded by Dr. Lee, and regularly carried, the above report was accepted. It was pointed out that the carrying out of the program would be under the direction of the Executive Committee and the House Committee.)

Adjournment, 5:00 p.m.

Attest: E. R. LOVELAND,  
Secretary

## ABRIDGED MINUTES, BOARD OF REGENTS

### SECOND MEETING

CHICAGO, ILL.

APRIL 29, 1947

The second meeting of the Board of Regents during the 28th Annual Session of The American College of Physicians convened at 12:30 o'clock, April 29, 1947, at the Palmer House, Chicago, with Dr. David P. Barr presiding, Mr. E. R. Loveland acting as Secretary, and the following in attendance:

David P. Barr	<i>President</i>
Hugh J. Morgan	<i>President-Elect</i>
James J. Waring	<i>1st Vice President</i>
A. B. Brower	<i>2nd Vice President</i>
T. Homer Coffen	<i>3rd Vice President</i>
William D. Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary General</i>
Maurice C. Pincoffs	<i>Editor</i>
Chauncey W. Dowden	<i>Chairman, Board of Governors</i>
E. L. Bortz	<i>Chairman, Advisory Committee on Postgraduate Courses of the Board of Governors</i>

Francis G. Blake  
James F. Churchill  
Reginald Fitz  
Roger I. Lee  
Charles T. Stone  
Walter B. Martin  
William S. Middleton  
James E. Paullin  
LeRoy H. Sloan  
George F. Strong  
Ernest E. Irons  
T. Grier Miller  
Charles F. Moffatt  
Charles F. Tenney

The Secretary read abstracted minutes of the previous meeting. The Secretary presented the following communications:

- (1) A letter from Dr. Archie M. Palmer, Director of the Patent Policy Survey Committee of the National Research Council, asking if The American College of Physicians has given consideration in its program or in its publications to the question of University Patent Policies and expressing his interest in discovering all available material on the subject, as well as research by educational and professional groups. The matter was opened for discussion.

DR. PINCOFFS: There appeared in the ANNALS about 10 years ago an editorial on this subject. It cannot be taken as an official statement of the College, however. At the time, there was a tendency to subsidize laboratories and there was a rather confused situation as to whom the results of the work belonged. The editorial tried to point out the dangers as well as the advantages, but it did not attempt to state the policy of the College. There is as yet no College policy as regards this question.

DR. LEE: This is a real controversial subject. People feel very strongly about it; threats of law suits are frequent. This should be referred to the Committee on Public Relations. It cannot be settled very simply or easily by the Regents.

PRESIDENT BARR: This communication will be referred to the Committee on Public Relations for consideration and report.

Communications Continued:

- (2) A letter, in two parts, from Dr. LeRoy H. Sloan, suggesting to the Board of Regents that on alternate years the College holds its meeting in an area which is not especially able to handle clinical meetings, and stating that he felt it a mistake to center the College meetings in purely clinical areas. By having alternate meetings clinical in nature and the intervening meet-

ings concentrated on morning lectures, panel discussions, and general sessions, Dr. Sloan felt that a wider selection of meeting places would be available and that the general interest of the College would be adequately or better served. The second suggestion was that the personnel of the Committee on Credentials be withheld from publication.

The discussion of the character of Annual Meetings was deferred for the third meeting of the Board of Regents, but the matter of the publication of the personnel on the Committee on Credentials was generally discussed. It was determined, by resolution, not to withhold the personnel of the Committee on Credentials from publication.

PRESIDENT BARR: May we now have the report of the Committee on the Annals of Internal Medicine, Dr. Fitz, Chairman.

DR. FITZ: The Committee reports that the ANNALS has had a successful year. The subscriptions have increased steadily, showing how popular is our editorial policy. Our financial health is blooming, almost in a manner that is pathological.

In 1932, there were 1,800 subscribers, in contrast to 10,000 for April, 1947. During 1946, \$28,146.00 was added to the general fund of the College from the operation of our periodical.

It must be emphasized, however, that these figures, besides revealing expert editorial management, also reflect abnormal times, for we have faced a continued paper shortage which has made it impossible to print as many pages and in as extensive a fashion as we would like. During January, February, and March of this year, 488 pages of reading material were printed, in contrast to 628 pages during the corresponding months in 1941. This means that the selection of material to be published has been chosen with most punctilious care, but, to offset that, a number of desirable articles either have been delayed in publication or have been rejected—a fact causing a certain amount of complaint and irritation in the minds of prospective contributors.

The cost of printing the ANNALS is increasing. Therefore, it seems reasonable to predict that our financial record will be far less spectacular when the journal regains its normal and desired size.

The Committee feels that the Editor's policies are wise. Last year an exceptional proportion of well-written and informative articles appeared, so that the method of their selection and the manner in which they have been edited have been admirable. The editorials have been instructive and have expressed a sound point of view. We now have about eighty exchanges, chiefly with medical periodicals published outside of North America. The establishment of a limited number of such exchanges, we believe, is important from the viewpoint of public relations and already has made many new friends for the College.

The Committee has discussed with the Editor the affairs of the ANNALS. The present salary levels and the cost of operation are satisfactory. As the journal enlarges, however, new problems are certain to arise. The office space occupied by the Editor is already in need of expansion, and a number of new developments are under consideration—developments such as the possibility of a more elaborate book review department, or entering the field of abstracting current articles of importance which appear in other medical periodicals, or of developing annual reviews on topics of general interest. Such matters lie in the future. At present, the Committee can only reiterate its pleasure in having the Editor back at his desk and its confidence in his wisdom and skill.

(On motion seconded and regularly carried, the above report was accepted.)

PRESIDENT BARR: You will next hear from the Editor, Dr. Pincoffs.

DR. PINCOFFS: Mr. President, Members of the Board of Regents: The Editor has nothing to add. He feels that he has been very handsomely dealt with in the preceding report.

I would like, however, to obtain expressions from the Board of Regents concerning the use of the Editorial section of the ANNALS as a medium for making public the policy of the College in questions of general interest to our membership.

At present the Editorial section is utilized chiefly to present brief topical reviews of recent work in the field of internal medicine. These are entitled Editorials and, judging by the requests received for reprints, they are popular with our readers.

Occasionally I have written editorials reviewing trends in medicine or in medical education. Occasionally in the past I have written editorials on controversial subjects such as the subsidization of medical research by industry or the certification of specialists, this last prior to the approval by the College of the principle of certification.

It is in regard to this last mentioned type of editorial, that which expresses the opinion of the Editor on a controversial subject in relation to which the College has no fixed policy, that I wish the opinion of the Regents.

As I now view this question, the Editor should not publish editorials on matters of policy without authorization from the governing bodies of the College since unescapably such editorials in the official College publication will be taken to express not the Editor's personal opinion but the College policy.

Personally I should like to see the College more active in developing its influence in the profession by formulating its approval or disapproval of many developments in the broad field of medical care which are subjects of controversy. I should like to see the Editorial section of the Annals utilized to make public the attitude of the College in these debatable questions.

Since at present the College has not organized itself to study such questions nor to exert its potential influence in determining their decision, I feel that an appropriate rule for the Editor to follow is to limit publication of editorials on questions of policy to such as have received the approval of the President and perhaps of the Board of Regents. I would appreciate expressions of opinion on this subject.

PRESIDENT BARR: This subject is open for discussion.

DR. FITZ: Would it not be possible to suggest, relating to editorials on matters which might be very much in the public mind and debatable, that the Editor adopt, as a matter of policy, the idea of submitting any proposed editorial to all the other members of the Editorial Board and to the President, and be guided by the editorial opinion of that group before publishing such an editorial as he might have in mind?

PRESIDENT BARR: It seems to me that we already have a system which Dr. Pincoffs has in mind which can be put into effect without any more formality than that.

We will now have a report from the Conference Committee on Graduate Training in Medicine by the Chairman, Dr. Fitz.

DR. FITZ: In December, 1939, the Regents established a special committee of two to confer with the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The aim of this Committee was twofold: To play a part in the work of hospital inspections so that residencies in medicine approved by the Council would meet with the approval of the Board and the College, and to serve as a source of information to the Regents in regard to various programs in the training of internists that might be established in medical schools or hospitals.

The Committee has not been inactive. The first problem it approached was that of developing a mechanism by which hospitals approved for resident training in medicine by the American Medical Association should also be approved by the Board of Internal Medicine and the College. When the Board first came into existence, considerable dissatisfaction was manifest. It was generally believed that many residencies in medicine approved by the Council were by no means approvable by the Board or the College and that, therefore, some uniform method of inspection and classification was desirable. This difficulty was surmounted by a simple agreement. The

Council agreed no longer to list residencies in medicine as approved unless they were also approved by the Board and the College. The machinery for inspection developed by the Council was not interfered with but the report of hospital inspections was sent to the Board and to the Conference Committee. Since that agreement was reached, no hospital residencies in medicine have been listed as approved by the Council unless they had also Board and College approval.

The War delayed the complete development of this program and necessitated a new and temporary makeshift. As the demand for resident training in medicine grew, many hospitals hitherto uninterested in education seemed to wish to play a part. The Council could not keep up with inspections at the rate the hospitals demanded and a large backlog accumulated which consisted of hospitals with residencies approved many years before and not recently re-inspected. An attempt was made to bypass some of these difficulties by the expedient of "temporary approval." Certain residencies in medicine that were guaranteed as being of adequate educational value by sources which the Committee and the Council and the Board regarded as reliable, were given "temporary approval." This method of getting work done has proved helpful. It must be emphasized, however, that such approval is only temporarily valid and may be denied when more formal inspections are made.

As the postwar program of residency training again becomes stabilized, the original plan should be resumed. A fair and accurate evaluation of the educational worth of any medical residency is essential. This is better obtained by the combined judgment of three such responsible agencies as the College, the Board, and the Council working together than by any one of these agencies working alone.

The Committee asks that this report be accepted as a report of progress. I move the existence of the Conference Committee continue for at least another year; its members being appointed by the President.

(The motion was seconded and opened for discussion.)

MR. LOVELAND: When this Conference Committee was first initiated, there were two members from the American Board of Internal Medicine and two members from the Board of Regents of The American College of Physicians for the purpose of sitting in with the Council on Medical Education and Hospitals at its meetings to review its inspectors' reports and finally to decide on whether a hospital shall be approved for resident training. The late Dr. Cutler, then Chairman of the Council, worked out a scheme by which the American Medical Association would use its machinery for the inspection of hospitals and the assembling of data, later to be considered at a joint meeting of the Council and the Conference Committee for action. This plan grew out of numerous requests coming to the College, asking the College to initiate a hospital inspection system comparable to that of the American College of Surgeons. It was the opinion of the Board of Regents of this College that a separate and additional certifying agency would duplicate in large part the work of the Council and that, therefore, the College should show its cooperative interest by participating with the Council through this Conference Committee. It was felt that such a plan would co-ordinate the standards and the objectives of the Council, the American Board and the College of Physicians.

DR. SLOAN: I would like to say that this technic is not in use at the present time.

MR. LOVELAND: No, Dr. Cutler's death and the War interrupted the consummation of the plan. Some of our Board will recall that back in the early 40's several members of our Board of Regents held a joint meeting with the Board of Trustees of the American Medical Association to discuss this whole matter, and thereafter, in numerous conferences with Dr. Cutler, the proposed plan was worked out.

DR. IRONS: When that matter was taken up, I was Chairman of the American Board of Internal Medicine. We found it difficult to get much action out of a Com-

mittee, even of six, and so the Conference Committee of six delegated to a representative of each group the duty of coming to a friendly agreement as to what should be done. Dr. Cutler, Dr. Hugh Morgan and I constituted that Committee. We obtained a very friendly working arrangement, with the Council being the inspecting agent. That was followed in the case of many, many hospitals which were inspected by the Council and passed on with the assistance of our Committee. Then came the War, Dr. Morgan was away, and I was no longer the Chairman of the Board. Dr. Cutler had died and, in the meantime, the record has been pretty well obliterated. I think your plan, Dr. Fitz, would be a very good one and probably you could re-initiate that close coöperative arrangement among representatives of the Board and of the College and of the Council.

DR. WARING: The present situation concerning recognition of hospitals for residencies is quite confusing. The Council on Medical Education has given a number of hospitals temporary approval pending the opportunity later to complete full inspection and appraisal. I feel that in some way we should be able to appraise this type of training more accurately, especially in view of the fact that our requirements are changing. The Board is not going to adhere rigidly to the old three-year period of graduate training and two years of practice, but is permitting substitution of certain things that take a little more time. This will recognize the importance of the experience that a young man is going to get in private practice, especially if he is under the tutelage of a competent, older man.

(The motion was put to a vote and carried.)

PRESIDENT BARR: The next Committee report is that on Fellowships and Awards by the Chairman, Dr. Fitz.

DR. FITZ: This report is divided into three distinct parts.

As has already been announced, the Committee has selected Dr. Fuller Albright of Boston as this year's recipient of the John Phillips Memorial Award.

Under special authority of the Board of Regents, the Committee has awarded five new Research Fellowships for the ensuing year, to wit:

- (1) Ward S. Fowler, 31 years old, a graduate of Harvard, who is to work on the pathologic physiology of certain pulmonary diseases at the Graduate School of Medicine, University of Pennsylvania.
- (2) Arnold L. Johnson, 33 years old, a graduate of McGill in 1940, who is to work on the hemodynamics of congenital heart disease at the Children's Memorial Hospital in Montreal.
- (3) Mary Ann Payne, 33 years old, a graduate of Cornell in 1945, who is to work on hepato-renal problems in shock and hypertension at the New York Hospital.
- (4) Miriam M. Pennoyer, 32 years old, a graduate of Rochester Medical School, who is to work in St. Louis on the function of the adrenal glands in the newborn.
- (5) Philip F. Wagley, 29 years old, a graduate of Johns Hopkins, who is to study certain mechanisms in hemolysis at the Thorndike Memorial Laboratory in Boston.

To this list should be added the name of Dr. Tom Fite Paine, Jr., who is to continue a Fellowship awarded a year ago so that he may further his studies in infectious diseases at the Thorndike Memorial Laboratory, where he is working with Dr. Maxwell Finland.

The Committee has reviewed the records of those who have received Clinical or Research Fellowships from the College. We are convinced that not only have such Fellows successfully promoted and advanced clinical research through oppor-

tunities opened to them by the College, but have also helped to maintain our high standards. Therefore, we believe that these Fellowships are an important College activity.

A review of the 1946-1947 record is as follows: Ten Clinical Fellowships were awarded and three Research Fellowships; a total sum of \$32,000.00 being allocated for their establishment. Of the Clinical Fellowships, three have been completed, four are still active, to end between June and November, and three of our Fellows resigned before completing their term of service. Of the three Research Fellowships, one has been completed, one is still active, to end in September, 1947, and one was not accepted. Of the total \$32,000.00 which might have been spent, \$5,667.00 has been unexpended.

On the 20th of October, the Board of Regents appropriated \$20,000.00 to guarantee not more than eight Research Fellowships for the ensuing year. The Committee has voted to expend only \$15,400.00 of this sum and to recommend that the residual unexpended \$4,600.00 be set aside in a special Fellowship Fund to be drawn on at some later date when special needs for Fellowship funds may be more urgent than they happen to be at present.

We are asking that the unexpended sum of \$20,000.00 that the Regents have voted to set aside for the purpose, be put aside in a special fund, because we feel at the present moment there are a lot of Research Fellowship funds around that can be obtained, and we believe that can't continue indefinitely, and we would like to suggest that a little fund for the purpose against bad days be built up.

I move the adoption of this part of the report.

(The motion was seconded by Dr. Waring. The question was called for, voted upon, and it was carried.)

Dr. FITZ: The next part of the report deals with the Alfred Stengel Memorial.

At the last meeting of the Board, no plans were proposed for the Alfred Stengel Memorial which Dr. Bruce hoped might be established as part of his legacy. The Committee makes the following recommendation:

There shall be established an award, known as the Alfred Stengel Memorial Award. This shall be awarded periodically by the President at a Convocation of the College to a Fellow—and preferably to a Fellow who has served as an Officer, Regent or Governor—who by virtue of his loyalty and service to the College deserves an honor from it that is unique. Besides loyalty and service to the College, the candidate shall have displayed an outstanding influence in maintaining and advancing the best standards in medical education, medical practice and clinical research, in perpetuating the history and traditions of medicine and medical ethics, and in upholding the dignity and the efficiency of Internal Medicine in its relation to public welfare. In brief, the award shall correspond to an Honorary Degree conferred by the College on those of its Fellows who have seemed most perfectly to have carried forward its aims and Dr. Stengel's ideals.

The recipient each year shall be chosen by the Board of Regents at a regular meeting prior to the Convocation at which the award is to be made. At least three and not more than five nominations shall be presented to the Board of Regents at their meeting at which the matter is to be considered. These nominations shall be made by a special committee appointed for the purpose by the President; it shall include the President and Secretary General ex-officiis, three members of the Board of Governors and two members of the Board of Regents. This Committee may make no nominations if appropriate candidates are not apparent. The Regents may have power of veto if, in their judgment, no one of the proposed candidates in any year is worthy of the proposed honor.

The Board of Regents shall make their selection by secret ballot. On the first ballot the two candidates receiving the greatest number of votes shall be chosen for

final vote. The candidate who finally receives the majority of votes shall be the recipient of the award at the next Convocation. No award shall be made unless the candidate thus selected is present to receive it. No announcement shall be made as to the name of the recipient so elected until after the award has been made.

The award shall be in the form of a diploma. This shall be designed by a Committee of three appointed by the President. The cost of its preparation shall be borne by the Bruce Fund.

The Committee recommends that that plan be established for the Alfred Stengel Memorial Award.

(The motion was seconded by Dr. Blake, was put to a vote, and was carried.)

DR. FITZ: The third matter is as follows:

The Committee has considered carefully how the residual income of the Bruce Fund—representing approximately \$200.00 per year—can best be spent. The following recommendation is made:

That until otherwise ordered, such income shall be added each year by the Treasurer to the sum appropriated by the Regents for Research Fellowships;

That each year the Committee on Fellowships and Awards shall select from the Research Fellows nominated the one who in their judgment offers greatest promise of attaining unusual distinction in investigation, teaching and as a clinician; and

That such Research Fellow shall be designated as the "Alfred Stengel Research Fellow of The American College of Physicians", stipend being paid in part from the income of the Bruce Fund.

I move the adoption of this recommendation.

(The motion was seconded by Dr. Lee, was put to a vote, and was carried.)

DR. FITZ: I move the adoption of the report as a whole, if that is possible.

PRESIDENT BARR: If there is no objection, the report will be adopted.

We will next have the report from the Committee on Finance, Dr. Charles Tenney, Chairman.

DR. TENNEY: The Committee on Finance met on April 28, 1947, with Dr. Charles T. Stone, Dr. Roger I. Lee, and the Chairman, Dr. Charles F. Tenney present, and with the Treasurer, Dr. William D. Stroud, and the Executive Secretary, Mr. Loveland, sitting in.

The Committee reviewed the Auditor's reports of College operations for 1946, copies of which are being distributed to the Board of Regents. Salient points include the following:

- (a) The Endowment Fund increased \$27,177.05, to \$223,373.89; the General Fund increased \$8,880.82, to \$234,159.26; total of both Funds, December 31, 1946, \$457,533.15;
- (b) Life Membership Fees for 1946 amounted to \$28,495.15; there was a realized profit on investments of \$1,981.90, and there was an addition of the James D. Bruce Memorial Fund of \$10,000.00;
- (c) The total income for the year was \$152,058.08; total expenses, \$138,072.17, leaving a balance of \$13,985.91; add to this the accrued interest on securities to December 31, 1946, \$1,552.91, and the net income of the General Fund amounts to \$15,538.82.

Detailed financial statements prepared by the Auditor and already in your hands will provide all information you may desire, and contain a certified registry of all investments.



The Investment Counsel report of February 26, 1947, discloses the following:

	<i>Endowment Fund</i>	<i>General Fund</i>	<i>Total</i>
Market Value .....	\$238,958.75	\$150,291.25	\$389,250.00
Book Value .....	229,261.74	147,538.28	376,800.02
Appreciation .....			\$ 12,449.98

The Finance Committee herewith reports to the Board of Regents the following additional purchases of securities for the Endowment Fund since January 1, 1947, and asks the approval of the Board of Regents. These purchases were made from available balances in the cash account of the Endowment Fund, and were approved by the Finance Committee, upon recommendation of our Investment Counsel:

10,000 United States Savings Bonds, Series "G", 2½'s .....	\$10,000.00
100 Shares, American Gas & Electric Co., common .....	4,035.03
100 Shares, Buffalo Niagara Electric, \$3.60, pfd. ....	10,185.00
	<hr/>
	\$24,220.03

The Committee has recommended to the Treasurer that we request the Investment Counsel, Drexel & Co., to have the College securities analyzed by a different individual from time to time, thus to get the benefit of new thought and analysis.

The Investment Counsel has requested the consideration of increasing their fee from \$200.00 to \$400.00 annually, but in view of the fact that actually the College investment portfolio has merely grown in volume of dollars, but not materially in the number of different securities, the Committee feels that it would be adequate if their fee were not increased more than \$100.00, instead of \$200.00, and has directed the Treasurer to consult them (Drexel & Co.) concerning this.

On recommendation of the Investment Counsel, dated April 18, 1947, the following investment changes are recommended, subject to the approval of the Board of Regents, since the accounts affect the Endowment Fund:

#### *Sale*

5,000 Chicago and Western Indiana RR Co., Consolidated,  
4's, 1952, at approximately 107;

#### *Purchase*

50 Shares, Atlantic Refining Co., \$3.75, pfd.;  
20 Shares, Liggett and Myers, common,

and the balance to be invested in U. S. Savings Bonds, series "G", 2½'s. These purchases include the investment not only of the proceeds of the balance from the Chicago and Western Bond, but also approximately \$6,800.00 cash balance now in the Endowment Fund.

The Committee is in receipt of notification from the Investment Counsel that we have received 100 Shares, Houston Light and Power Co., common, due to a two-for-one split of our holdings in that security—this being paid as a stock dividend.

The Committee recommends to the Board of Regents an additional appropriation of \$200.00, to be added to the President's budget for the current year.

The income of the College since January first of the current year has materially increased from dues and Life Membership subscriptions. Already some \$48,000.00 has been collected from dues and \$21,000.00 from Life Membership subscriptions. These exceed considerably our estimated income prepared last autumn. The Committee reports to the Board of Regents that the present balance in the General Fund is adequate to cover the building program, should the Executive Committee go forward with it, without disturbing any investments of the College.

PRESIDENT BARR: You have heard Dr. Tenney's report. Is there a motion to adopt it?

DR. IRONS: I would like to say that this is a most excellent report, and no question could be raised in criticism of it. Also the expenditure for Fellowships is highly desirable because the College has educational activities as its principal function. I think I remember, though, that here about a year ago when the appropriation of \$32,000.00 was made for Fellowships, that this total amount exceeded the visible receipts as estimated for the coming year. I wonder if that was a good act? Fortunately, there were receipts which were unexpected and, therefore, no deficit developed.

I speak of these things because I have just been through another period in another organization, the American Medical Association, where there was the same kind of situation, only in a little larger amounts. Both organizations are eminently sound financially. It is just a question of policy. I know that to raise such a question is not a very popular thing to do, but I think the Board ought to think of that side of it. No budget should be passed which does not come within the prospective income.

One other matter, the College is an expanding and rapidly growing institution. There are now over 6,100 members. Whenever an organization or business grows, its financial obligations increase and, consequently, it needs an increase in its available quick assets, and also in its working capital. That is a general, recognized principle. Now, we have, it is true, a very pleasant financial report, due to the care of the Finance Committee and the Treasurer. But it seems to me that it might be a good plan if you could prepare a little for the coming depression, which is bound to hit us. There is no mechanism that has ever been devised to prevent this up and down movement of business. Our business must go on whether there is a depression or not. We ought to build up some reserve to meet such a contingency, which will surely arise.

As a beginning of that, I wonder if it would not be wise to have set up a reserve fund? At present you could call it a Building Reserve. Of course, we would spend it if things go right, but we might set up a Building Fund for \$50,000.00, and name another reserve a little later, so that we don't have so much free money; and don't put it in the Endowment Fund, but keep it more for liquid use, at the discretion of this Board.

I know that it is just bookkeeping, putting it from one pocket to another, but it does have a very restraining and favorable effect on the attitude of spending bodies, when some of these funds are put away with a little bit of an earmark.

(Upon motion regularly made, seconded, and carried, the report of the Committee on Finance was accepted.)

PRESIDENT BARR: May we now have the report of the Advisory Committee on Postgraduate Courses, Dr. E. L. Bortz, Chairman.

Dr. Bortz spoke at some length on the objectives of the Advisory Committee on Postgraduate Courses and outlined the courses proposed on the schedule for the autumn of 1947 and some of the courses on later schedules for 1948. He brought up for discussion the matter of the matriculation fee for the courses. Previously, the standard fee in the College had been \$20 for members and \$40 for non-members. In comparison with fees charged by various medical schools and institutions, the College fees were thought to be quite too low. Therefore, the Committee recommended that the fee be increased to \$30 per week for members, \$25 of which shall go to the Director of the course and the institution and \$5 of which shall be retained by the College to help cover administrative expenses. Dr. Bortz further stated that the Committee is interested in broadening the basis of training in these courses and will add more and more basic science data to the content thereof. He stated also that many other medical bodies and groups of higher learning in specialized fields have consulted the College concerning the manner in which our program is conducted and, in many instances, have copied in large measure our whole plan of instruction. He said that

the Committee is somewhat disturbed by the fact that there is such a demand for the courses that the College is unable to accommodate many. He said also that the Committee favors the reduction in the size of the classes to 25 or 30 physicians and that it has been due only to the pressure of registrants that classes temporarily have been very much larger in many instances. The Committee has continued to receive the active and enthusiastic support of the various faculties of medicine over the country and also offers, from time to time, from institutions that wish to participate. Dr. Bortz said it appears there is a certain amount of recognition that is bestowed upon the directors and the institutions selected for the College courses and that the reaction is quite favorable. The letters and reports from those who take the courses have been very helpful for the guidance of the Committee in improving and extending its program. These reports are summarized and offered to the Directors for further improvement in their particular courses.

Dr. Bortz' report was accepted by the Board of Regents.

PRESIDENT BARR: May we have a further report from the American Board of Internal Medicine through its Chairman, Dr. Waring.

DR. WARING: To finish up my unexpired term of two years, the American Board submits to your wisdom the following list of names:

Dr. Walter L. Palmer	Chicago, Ill.
Dr. Chester M. Jones	Boston, Mass.
Dr. Henry M. Thomas, Jr.	Baltimore, Md.
Dr. Frank B. Kelly	Chicago, Ill.
Dr. George R. Herrmann	Galveston, Texas

One of these should be selected to fill my unexpired term. Then the Board would like to recommend that Dr. William S. McCann be reelected for a term of three years; Dr. William B. Porter and Dr. Cecil J. Watson each be reelected for a term of three years. Dr. McCann is the newly elected Chairman of the Board. Dr. Hugh Morgan is the newly elected Vice-Chairman of the Board. All these elections should start on July 1, 1947.

(On motion by Dr. Fitz, seconded by Dr. Tenney and unanimously carried, Dr. McCann, Dr. Porter and Dr. Watson were re-nominated for a term of three years, beginning July 1, 1947.)

(The Secretary was instructed to conduct a written, secret ballot for the election of the successor to Dr. Waring and after the ballots were counted, Dr. Walter L. Palmer was declared nominated to fill Dr. Waring's unexpired term.)

Dr. A. B. Brower, 2nd Vice President, temporarily assumed the Chair and called for a report from the Committee on Educational Policy.

DR. MIDDLETON: The Committee on Educational Policy met with the Advisory Committee on Postgraduate Courses and agreed in principle in all matters there considered, and, therefore, has no separate report to render.

CHAIRMAN BROWER: Dr. Irons, you have a report on the Joint Committee for Coördinating Medical Services.

DR. IRONS: This Joint Committee was originally organized as a war-time measure under the Chairmanship of Dr. Roger Lee and it was his organizing ability that gave it its good start. The membership was first confined to The American College of Physicians, the American College of Surgeons, and the American Medical Association. It then became evident that it would be helpful to get a wider representation and so from time to time other organizations were added, including the Army, Navy, Public

Health Service, Veterans Administration, the American Red Cross, the Council on Medical Education, the Committee on Rural Medical Service, the Pharmaceutical Association, the Committee on Economics, the Federal Security Agency, the Association of American Medical Colleges, the Federation of State Medical Boards and the Advisory Board on Medical Specialties. Meetings were continued during the War and at the close of the War, it was decided to continue the organization as a sort of forum for American medicine where any question could be discussed and opinions elicited, having in mind that this Committee has absolutely no elective function, but is merely an exploring agency to observe and comment and to influence public opinion. Under this program a number of matters have been considered, such as the organization of the Veterans Administration, Surplus Property Disposal, Red Cross Blood Service, residency opportunities for returning veterans—there are some 10,000 residencies available now, where there were formerly only about 5,000—the distribution of medical services over the nation, the re-organization of the medical departments of the Army and Navy. All of these problems have come up before the Committee and the minutes are published in the journal of the American Medical Association and rather widely read.

(On motion by Dr. Fitz, seconded and carried, Dr. Irons' report was accepted.)  
(President Barr resumed the Chair.)

PRESIDENT BARR: We have received letters from Drs. Ernest Bradley, John Musser, and Sydney Miller, new Masters of the College who are unable to be here because of illness. I think it would be very nice indeed if this Board could send an appropriate message to each of these Masters, and if it is so ordered, I will accept the responsibility of sending appropriate messages on behalf of the Board. If there is no objection, that will be done.

Our Board has been asked on numerous occasions this year to send participants to various UNESCO meetings. I have asked Dr. Waring to represent us at a meeting to be held in Denver.

Since this is the last meeting of the present Board, I would like to express to all my appreciation of the coöperation that I have received from every member of the Board. Thank you very much indeed. (Applause.)

(The meeting adjourned at 3 o'clock.)

Attest: E. R. LOVELAND,  
*Secretary*

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## ABRIDGED MINUTES, BOARD OF REGENTS

### THIRD MEETING

CHICAGO, ILL.

MAY 2, 1947

The third meeting of the Board of Regents of The American College of Physicians during its 28th Annual Session was held at the Palmer House, Chicago, on Friday, May 2, 1947, at 1:00 p.m., with Dr. Hugh J. Morgan, the new President, presiding and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Hugh J. Morgan	<i>President</i>
Francis G. Blake	<i>2nd Vice President</i>
Charles T. Stone	<i>3rd Vice President</i>
Walter L. Palmer	
Walter B. Martin	
James E. Paullin	
LeRoy H. Sloan	
George F. Strong	
Ernest E. Irons	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	
David P. Barr	
A. B. Brower	
Alex. M. Burgess	
Ernest H. Falconer	

## Visitors:

James B. Herrick  
William J. Kerr

PRESIDENT MORGAN: I am sure all of the members of the Board who have served prior to this meeting would want to welcome to the Board Dr. Alex. M. Burgess, Dr. Ernest H. Falconer, Dr. Cyrus C. Sturgis and the new Chairman of the Board of Governors, Dr. Walter L. Palmer. The minutes of the last meeting have been abstracted and reviewed by the Secretary and myself and there is nothing requiring action of this Board today, and unless there is some objection, we will not have the minutes read.

In accordance with regulations of the Constitution and By-Laws, Dr. George Morris Piersol was reelected Secretary-General, and Dr. William D. Stroud was reelected Treasurer. The following were formally elected as the Executive Committee of the Board of Regents:

\*Hugh J. Morgan  
Walter W. Palmer  
George Morris Piersol  
William D. Stroud  
Francis G. Blake  
Ernest E. Irons  
James E. Paullin  
George F. Strong  
Charles F. Tenney

Likewise, in accordance with various regulations of the Constitution and By-Laws, or of the Board of Regents, the personnel of all standing Committees was appointed. (The personnel of these Committees has already been published in a preceding issue of this Journal and are not herewith repeated.)

PRESIDENT MORGAN: We shall now proceed to select the 1948 meeting place, dates of the meeting and appointment of the General Chairman.

\* Chairman.

(Before receiving the invitations, Mr. Frank Power of the Chicago Convention Bureau extended his thanks to the College for coming to Chicago, stated it had been a pleasure to work with the Officers and the Committees and expressed the hope that the College would return in the not too distant future.)

(Mr. Walter Swanson, Vice President of the San Francisco Convention Bureau, presented an official invitation, delineated the facilities of the city, its Convention Hall, its hospitals, its medical schools, and other agencies, and made guarantees with regard to adequate meeting facilities and hotel rooms. He promised full and complete assistance in arranging all details of the meeting and insuring a successful convention. Numerous questions were asked by Board members, which Mr. Swanson answered and then retired. After general discussion and comparison of the facilities and conditions of a meeting in San Francisco with those earlier presented from New York City, and in discussion with Dr. William J. Kerr and Dr. Ernest H. Falconer, on motion by Dr. Blake, seconded by Dr. Tenney and unanimously adopted, San Francisco was selected for the 1948 session during the period April 19-23, inclusive. Likewise, by resolution, Dr. William J. Kerr and Dr. Ernest H. Falconer were nominated and elected Co-Chairmen of the Session.)

(On motion by Dr. Paullin, duly seconded and carried, the President, General Chairmen, and the Executive Secretary were given full authorization to complete all necessary arrangements in regard to the 1948 Annual Session.)

There was a general discussion by Dr. Paullin concerning the possibility of the College sometime holding its Annual Session in a city which might not have the usual clinic facilities but which could conduct a very excellent meeting with reduced clinics but with an increased program of panel discussions, morning lectures, and general sessions. It was pointed out by Dr. Sloan, General Chairman of the Chicago Session, that some clinicians at the meeting felt that their programs were competing with the morning lectures, which accounted, in some instances, for the small attendance at the clinics. Some felt that the College in its enthusiasm provided too abundant clinic facilities and should not expect every hospital to participate. The increasing popularity of the excellent morning lectures makes the larger clinic facilities unnecessary, although there is a continuing demand for real clinics where patients are shown. Dr. Paullin expressed the hope that an Annual Session of the College might be held in Atlanta in 1949, or later, providing a survey of facilities justified an invitation.

(On motion by Dr. Tenney, seconded by Dr. Irons, and carried, the Board of Regents went on record as expressing the opinion that the inclusion of clinics in the program is not a necessity.)

PRESIDENT MORGAN: Is there any other business to be presented?

DR. BARR: Mr. President, may I present a resolution to the Board?

"RESOLVED, that the Board of Regents of The American College of Physicians expresses its appreciation to Dr. Edward L. Bortz, a distinguished Fellow of this College, for his tireless energy, exceptional ability and broad vision in developing and organizing the Postgraduate Courses conducted so successfully under the auspices of The American College of Physicians.

"Furthermore, the Board of Regents extends to Dr. Bortz its hearty congratulations upon his elevation to the Presidency of the American Medical Association, a well-deserved honor which brings distinction not only to him, but also to The American College of Physicians, that he has served so long and faithfully."

(A motion was regularly made and seconded to adopt the resolution and it was put to a vote and carried.)

Adjournment—2:30 o'clock.

Attest: E. R. LOVELAND,  
Secretary

## GENERAL BUSINESS MEETING

CHICAGO, ILL.

MAY 1, 1947

The Annual General Business Meeting of The American College of Physicians convened at the Palmer House, Chicago, at 2:15 p.m., May 1, 1947, Dr. David P. Barr, President, presiding. Abstracted minutes of the previous General Business Meeting were read by the Secretary, Mr. E. R. Loveland, and accepted by resolution.

The Treasurer, Dr. William D. Stroud, presented the following Annual Report:

"Mr. President, Fellows and Masters of the College: The College accounts have been audited by a Certified Public Accountant for 1946, and the final report will be published to the members through the pages of the ANNALS OF INTERNAL MEDICINE.

"During the year 1946, the College added to its Endowment Fund \$27,177.05, chiefly through Life Memberships, and to the General Fund \$8,880.82, or a total of \$36,057.87. This brought our assets, as of December 31, 1946, to a total of \$457,533.15, of which \$223,373.89 represents the Endowment Fund and \$234,159.26 represents the General Fund.

"The College operated entirely within its budget for the year. Our investments are carefully watched by our Investment Counselor and the Committee on Finance and are in a favorable condition. As of January 1, 1947, the College held investments at book value, totalling for the Endowment Fund \$229,261.74, and for the General Fund, \$147,537.28, or a total of \$376,799.02. These securities, according to present market value, show an appreciation of \$12,449.98.

"The Board of Regents has approved a budget for 1947 calling for an estimated income of \$165,700.00 and an estimated expenditure of \$162,396.61, leaving an anticipated balance slightly exceeding \$3,000.00. It is, however, reasonable to anticipate that with the rapid growth in the circulation of our journal and the marked increase in Life Membership, that the surplus will be materially greater.

Respectfully submitted,

WILLIAM D. STROUD, *Treasurer*"

(The report of the Treasurer was formally accepted by resolution.)

Mr. E. R. Loveland presented the following Annual Report of the Executive Secretary:

"Mr. President, Fellows and Masters: My report is supplementary to those of the Treasurer, the Secretary-General and the President. With the advent of peace, the 35 per cent of our members who were in the Armed Forces have, in very large measure, returned to civilian activities. We are gratified to have them returned to active participation in the College. There has been an enormous increase in the volume of College activities, in the past year; as an illustration, the circulation of the ANNALS OF INTERNAL MEDICINE has grown not only in North America, but throughout the world, until it now has reached 10,000, which is greater than that of any other journal in our field, including those of much greater age.

"Naturally, there has been a great impetus in membership activities and in the number of candidates seeking membership.

"Our Regional Meetings program is now centering around the individual and more personal type of State meeting. Since the last Annual Session, nineteen Regional Meetings have been held in various parts of the United States, with an

attendance representing at least 50 per cent of the College membership. Six of these meetings were of the multi-State character.

"A year ago we proposed to republish the complete Directory of the College, but conditions were such that paper was not available and the costs were prohibitive. Therefore, a new Membership Roster was published as a substitute, until such time as we can revise and publish a full Directory.

"During the past year, Mr. F. V. L. Pindar has been added to the staff of the College as my assistant, and the secretarial staff has been increased.

"We are approaching that time when our present building has insufficient facilities for our work, and the Board of Regents, with the House Committee, is considering plans for an appropriate and adequate addition to our building.

"Those of you who have not yet done so are especially invited to visit the College Booth, where many interesting facts about the College are on display.

"I have just received from our registration desk a report that the total registration at this moment is 4286,\* of which 609 are visiting ladies.

Respectfully submitted,

E. R. LOVELAND, *Executive Secretary*"

(The report of the Executive Secretary was accepted by resolution.)

Dr. George Morris Piersol presented the following Annual Report of the Secretary-General:

"Mr. President, Officers, Regents, Masters and Fellows of the College:

"*Membership*: Since the last Annual Session of the College, there have been elected four Masters, 231 Fellows and 396 Associates, which brings the total membership up to 6,179, divided as follows:

8 Masters
4,516 Fellows
1,655 Associates
<hr/>
6,179 Total

"*Life Members*: During the past year, 124 additional Fellows have become Life Members of the College, bringing the total up to 612, of whom 46 are deceased, leaving a balance of 566.

"*Deaths*: It is with regret we report the deaths of 66 Fellows and 10 Associates during this period. Their names have already been recorded in the Archives of the College.

"*Postgraduate Courses*: The Advisory Committee on Postgraduate Courses has been even more active during the past year than heretofore. Through their efforts, there have been organized 23 separate and distinct courses distributed among 22 universities, hospitals and other institutions throughout the country. One thousand twenty-three doctors have taken advantage of these courses, an evidence of their increasing popularity and value.

"*Fellowships*: A further important educational activity of the College has been the creation and extension of Clinical and Research Fellowships. For the calendar year 1946 there was an appropriation of \$32,500.00, providing for 10 Clinical Fellowships and three Research Fellowships. For the calendar year 1947, \$20,000.00 additional has been appropriated for Research Fellowships. Seven new Fellowships were awarded to begin on July 1, 1947, or shortly thereafter.

\* Final registration later recorded, 1,694 members; 1,382 guest physicians; 70 guest non-physicians; 137 senior and graduate students; 518 exhibitors; 609 ladies; total, 4,410.



"As gratifying as are the above mentioned educational activities of the College, it should not be overlooked that the most significant and far-reaching contribution of the College is its Annual Clinical Session. Since their inception, these Sessions have been marked by progressively increased interest and ever widening scope. The present Clinical Session is an outstanding example of what may be accomplished by a year's well coordinated effort. The College is mindful of its great debt to those who have made this Chicago Session possible. Through their example, they have set a pattern to be followed, one which gives assurance of what the future of the College holds in store.

Respectfully submitted,

GEORGE MORRIS PIERSOL,  
*Secretary-General*"

"And now, President Barr, since you assumed office a year ago at Philadelphia, those of us whose privilege it has been to work with you have been inspired by your leadership. You have become endeared to us by reason of your fairness and the foresight with which you have handled the affairs of the College. Therefore, it is my pleasure and privilege, on behalf of your fellow Officers, Regents and Governors of the College, to present to you this Gavel, an enduring token to show our appreciation and the esteem in which we regard you, and to thank you for the admirable way in which you have guided the College through your term of office." (Applause.)

(Dr. Piersol then presented the Gavel to President Barr.)

PRESIDENT BARR: I shall treasure this Gavel as a symbol of a happy year, a year of opportunity to serve the College in which I have great faith and for which we all have high hopes. A realization of the distinction of my predecessors made me approach this year with great humility. Like them, I have done my best to advance the purposes of the College, and at the end of my term, I realize how little I have accomplished and how far it falls short of my estimation of the honor. Anyone who has been an Officer of The American College of Physicians realizes that our management is very sound. Presidents may come and may go, but Mr. Loveland goes on forever. It is fortunate for the College that it is so. He brings to his position the long experience in business of fine judgment and unselfish devotion. All of the arrangements, schedules, agenda, etc., are prepared with such precision that one is not aware of difficulties nor the immense amount of detail which they involve.

To the Committees that carried on the work this year, I wish to express my gratitude, especially to Dr. Reginald Fitz and the Committee on Fellowships and Awards of which he has been Chairman, charged with the selection of six Research Fellowships and the formulation of the James D. Bruce Lectureship and the Alfred Stengel Memorial Award.

The chief task for the President each year is to arrange the Annual Session. This year the arrangements have been made easy and delightful by the extraordinary efficiency and imagination of Dr. LeRoy H. Sloan, the General Chairman, and the fine work which all of his Committees have done over the months preceding this meeting.

In relinquishing the Presidency of the College, it is a pleasure to me to have Dr. Hugh J. Morgan to follow. He has been my friend for many years. I know his sagacity, his dignity, his unfailing kindness, his sense of fitness, and all of you know of his outstanding War record, his eminence as an educator and adviser. The College is, indeed, fortunate to have such a servant to guide its policies during the coming year. I welcome Dr. Morgan. (Applause.)

(President-Elect Dr. Hugh J. Morgan assumed the Chair.)

PRESIDENT MORGAN: I appreciate Dr. Barr's more than generous introduction and your more than cordial reception. I believe I know how Uncle Zeke felt on Judgment Day. During his life Uncle Zeke had been a carousing, lazy fellow and a wicked

man. On Resurrection Day, as he came up from his grave, he read on the tombstone, "Here lies an industrious, temperate man of God." Said Uncle Zeke, "Excuse me, boys, Ah don come up out of de wrong hole."

The chief reason for having Officers at the helm in this College, an educational institution, is to provide personnel for the administration of the business of the College; and, in that spirit, I shall forego this opportunity to express my deep appreciation and will pass on to new business.

The first item to which you must give consideration is certain amendments to the By-Laws which have been approved by the Board of Regents, published in the ANNALS and are now being submitted for adoption by the Masters and Fellows of the College. They will be read by Mr. E. R. Loveland, Executive Secretary.

MR. LOVELAND: The first is an amendment to the By-Laws, Article IV, Section 2, the following paragraph to be added:

"The members of the Board of Governors shall each serve for a term of three years and not more than three consecutive terms."

(Upon motion regularly made, seconded, and carried, it was voted to adopt the above amendment.)

MR. LOVELAND: The following are proposed revisions and amendments of Article V, the insertion of a new Article VI, revision and amendment of old Article VI now becoming Article VII, and with re-numbering of old Articles VII to XIV, inclusive, the new numbers becoming Articles VIII to XV, inclusive:

#### "ARTICLE V

##### "Election of Fellows

"Section 1. A Fellow of the College shall have met the following qualifications and requirements:

"(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

"(b) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

"(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine or an allied specialty at a permanent location for at least three years preceding nomination for Fellowship. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

"(d) The criteria of eligibility for election to Fellowship are bilateral:

"1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

"2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation,

however, shall not apply to candidates from civilian life who were elected to Associateship prior to April 6, 1940, nor to such candidates from the Army, Navy and Public Health Service who were elected prior to and including April 1, 1944.

#### "Proposal

*"Section 2.* His name shall be proposed in writing by a Master or Fellow of the College from the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration, or, in special instances, by an officer of the College or by a member of the Board of Regents. His nomination must be accompanied by an adequate written statement made both by the proposer and the seconder, containing all of the above cited qualifications of the candidate. Furthermore, the name of the candidate shall be sent to each Fellow in the candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials.

*"Section 3.* The credentials of the candidate shall be considered by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

"Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary-General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

*"Section 4.* Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preeminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be further considered: maturity, national reputation, publications and other contributions to medical science and public welfare. The Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship.

"This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

#### "ARTICLE VI

##### "Election of Masters

*"Section 1.* A special Committee on Masterships will be named by the President. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Master to the Board of Regents for election or rejection.

#### "ARTICLE VII

##### "Election of Associates

*"Section 1.* An Associate of the College shall have met the following qualifications and requirements:

- "(a) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.
- "(b) After receiving his medical degree, the candidate shall have had at least one year internship in an approved hospital and three years of organized graduate training in internal medicine or allied fields, or its equivalents, approved by the Committee on Credentials and the American Board of Internal Medicine. One year of this graduate training may be spent in the basic sciences.
- "(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions.
- "(d) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to confine his practice to internal medicine or an allied specialty from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official institutional position in internal medicine, an allied branch of internal medicine or in medical research.

#### "Proposal

"*Section 2.* His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration; or, in special instances, by an officer of the College or by a member of the Board of Regents.

"*Section 3.* The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

"Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

#### "Term of Associateship and Eligibility for Fellowship

"*Section 4.* Candidates so elected shall be continued as Associates for a term not to exceed five years.

"An Associate will be eligible for election to Fellowship at the end of three years. Upon expiration of this three-year period, he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next two years, provided he has met the requirements necessary for Fellowship within that time. If he is not elected to Fellowship within five years, his Associateship is automatically terminated. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions."

(By motion regularly made, seconded and carried, the above amendments were fully adopted.)

PRESIDENT MORGAN: We shall now hear from the Committee on Nominations, Dr. James J. Waring, Chairman.

DR. WARING: Mr. President, Officers, Fellows and Masters of the College: In accordance with the provisions of the Constitution and By-Laws, the Nominating Committee has placed in nomination and has published in the ANNALS OF INTERNAL MEDICINE the names of nominees for the elective offices as given below and is also placing in nomination the following names for the Board of Regents and the Board of Governors. These nominations do not preclude nominations that may be made from the floor.

"I. Elective Offices:

"President-Elect ..... Dr. Walter W. Palmer, New York, N. Y.  
 First Vice President ..... Dr. Reginald Fitz, Boston, Mass.  
 Second Vice President ..... Dr. Francis G. Blake, New Haven, Conn.  
 Third Vice President ..... Dr. Charles T. Stone, Galveston, Tex."

(President Morgan, after asking for nominations from the floor, of which there were none, called for a vote and the nominees above presented were by resolution regularly elected.)

DR. WARING:

"II. For the Board of Regents, term expiring, 1950:

"Dr. David P. Barr ..... New York, N. Y.  
 Dr. Alexander M. Burgess ..... Providence, R. I.  
 Dr. Ernest H. Falconer ..... San Francisco, Calif.  
 Dr. Cyrus C. Sturgis ..... Ann Arbor, Mich.  
 Dr. A. B. Brower ..... Dayton, Ohio"

(President Morgan called for nominations from the floor, of which there were none, and by resolution the above nominees were regularly elected.)

DR. WARING:

"III. For the Board of Governors, term expiring, 1950:

"Dr. Arless Arland Blair, Fort Smith ..... ARKANSAS  
 Dr. Dwight L. Wilbur, San Francisco ..... CALIFORNIA (Northern)  
 Dr. Benjamin F. Wolverton, Cedar Rapids ..... IOWA  
 Dr. Edgar Hull, New Orleans ..... LOUISIANA  
 Dr. Douglas Donald, Detroit ..... MICHIGAN  
 Dr. Edgar V. Allen, Rochester ..... MINNESOTA  
 Dr. Ralph A. Kinsella, St. Louis ..... MISSOURI  
 Dr. Lawrence Parsons, Reno ..... NEVADA  
 Dr. Harry T. French, Hanover ..... NEW HAMPSHIRE  
 Dr. George H. Lathrope, Newark ..... NEW JERSEY  
 Dr. Paul F. Whitaker, Kinston ..... NORTH CAROLINA  
 Dr. Robert B. Radl, Bismarck ..... NORTH DAKOTA  
 Dr. Herman A. Lawson, Providence ..... RHODE ISLAND  
 Dr. Robert Wilson, Jr., Charleston ..... SOUTH CAROLINA  
 Dr. Ellsworth Lyman Amidon, Burlington ..... VERMONT  
 Dr. J. Edwin Wood, Jr., Charlottesville ..... VIRGINIA  
 Dr. George Anderson, Spokane ..... WASHINGTON  
 Dr. Delivan A. MacGregor, Wheeling ..... WEST VIRGINIA  
 Dr. Arthur B. Walter, St. John ..... MARITIME PROVINCES  
 Dr. Arthur T. Henderson, Montreal ..... QUEBEC  
 Dr. José J. Centurión, Havana ..... CUBA"

These nominations have been respectfully submitted by the Committee on Nominations, George F. Strong, Ralph Kinsella, Asa L. Lincoln, Jonathan Meakins, James J. Waring, Chairman.

(President Morgan asked for nominations from the floor, of which there were none; by resolution the above nominees were regularly elected to the Board of Governors.)

(President Morgan called for President-Elect Dr. Walter W. Palmer to be conducted to the platform, but it was determined that due to delay in air travel. Dr. Palmer had not yet arrived.)\*

PRESIDENT MORGAN: I am calling on Dr. Waring to present a resolution of appreciation and thanks to all those who have made this such a wonderful meeting.

DR. WARING: Mr. President and Members of The American College of Physicians: In your names I would like to propose a vote of thanks and keen appreciation to all the following persons who have contributed so greatly to the success of our Scientific Sessions and the ever-to-be-remembered pleasures of this meeting in Chicago:

To our distinguished leader and President, Dr. David P. Barr, for the inspiration of his guidance during the past year, as well as during this meeting; to his Chief of Staff, General Chairman LeRoy H. Sloan, for a magnificent job; to Dr. Howard Wakefield, Chairman of the Chicago Committee on Arrangements; to Dr. Walter L. Palmer, Chairman of the Committee on Clinics; to Dr. Willard O. Thompson, Chairman of the Committee on Panel Discussions; to Dr. Edwin P. Jordan, Chairman of the Committee on Publicity; to Mrs. Thomas J. Coogan, General Chairman of the Committee on Ladies' Entertainment, and all of the lovely ladies on her Committee—to Mrs. LeRoy Sloan, Mrs. Grant Laing, Mrs. Clifford J. Barborka, Mrs. James Hutton, Mrs. Chauncey C. Maher, Mrs. Gilbert H. Marquardt, Mrs. C. Phillip Miller, Mrs. Walter L. Palmer and many others; to the Coöperating Committee of the Chicago Hospitals and other institutions; to civic bodies and local institutions, who opened their doors to our members and their ladies; to the Management of the Palmer House; to Mr. Frank Power of the Chicago Convention Bureau; and last, but not least, to Dr. Clifford J. Barborka, Chairman of the Committee on Entertainment, for bringing "Harvey" to our party; to all these and many others, individually and collectively, our heart-felt thanks again for their generous hospitality in full measure—pressed down and running over.

(There was a standing vote of thanks, in which the members rose and applauded.)

Adjournment—3:00 o'clock.

Attest: E. R. LOVELAND,

*Secretary*

\* Dr. Palmer arrived just at the close of the Business Session and made a short Inaugural Address at the following General Scientific Session.

## OBITUARIES

## DR WILLIAM EMMETT GARDNER

Dr. William Emmett Gardner, F.A.C.P., died at his home in Louisville, Ky., on April 8, 1947 from coronary artery disease. Dr. Gardner was born in Sonora, Ky., August 24, 1877. He received the degree of Bachelor of Arts from Georgetown College in that state in 1899, and the degree of Doctor of Medicine from the University of Louisville School of Medicine in 1902. He subsequently undertook postgraduate studies in New York, Chicago, Boston, and Cleveland.

Dr. Gardner was a diplomate of the American Board of Psychiatry and Neurology. He held appointments as Psychiatrist and Neurologist in the Norton Memorial, St. Joseph's, Kentucky Baptist, and Louisville General Hospitals. He was also Consultant to the Louisville Neuropathic Sanatorium. He served for a time as a member of the Board of Examiners of the American Psychiatric Association. He returned to the University of Louisville School of Medicine as a member of the teaching staff and attained the position of Clinical Professor of Psychiatry and Head of the Department.

Dr. Gardner was a member of the American Association for the Advancement of Science, the Southern and Kentucky Psychiatric Associations, the Jefferson County Medical Society, Medico-Chirurgical Society of Louisville, Southern Medical Association, Kentucky State Medical Association, and the Louisville Society for Mental Hygiene, as well as a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians in 1926.

In reporting Dr. Gardner's death, a Louisville newspaper spoke of him as a "pioneer in introducing modern treatment of mental illness in his native State."

C. W. DOWDEN, F.A.C.P.,  
Governor for Kentucky

## DR. THOMAS LAIDLAW SHEARER

On December 13, 1946, the College lost one of its oldest members in the death of Dr. Thomas Laidlaw Shearer, F.A.C.P., of Baltimore, Md. In his passing, we have lost one of the old school; rich in culture as well as medicine.

Dr. Shearer was born February 13, 1859, at Philadelphia, Pa. He received his early education in Baltimore at the Friends Elementary School

and at Johns Hopkins University. For his further education, he went abroad and in 1882 received the degrees of M.A., M.B., C.M., from the University of Edinburgh. The following year he devoted to medical studies in Vienna.

He began his practice of medicine in Baltimore in 1885 in his father's office. During his professional career Dr. Shearer cared for patients in the Women's Hospital, Union Protestant Infirmary, Mercy Hospital, St. Agnes Hospital, Crippled Children's Hospital School. During World War I, he was Acting Medical Examining Officer at Baltimore for the British and Canadian Armies. He also held a reserve commission in the Medical Corps, U. S. Army, as consultant.

Dr. Shearer was a Fellow of the American Medical Association, and a member of the Maryland Academy of Sciences. He was greatly interested in art and was a member of the Municipal Art Society of Baltimore. He also maintained membership in the University of Edinburgh Club of North America.

Dr. Shearer was one of the earliest members of the American College of Physicians, having been elected to Fellowship in 1917.

WETHERBEE FORT, M.D., F.A.C.P.,  
Governor for Maryland

### DR. HARRY AUGUST BRANDES

Dr. Harry August Brandes, F.A.C.P., died on May 12, 1947, of multiple myeloma at the age of 59 years, after an illness of about seven years. He was born near Granite City, Ill., November 8, 1887, and was graduated from the Washington University School of Medicine, St. Louis, Mo., in 1912. Coming to North Dakota in 1914, he practiced at Hebron and also at Hazen. He served as a medical officer in World War I. Thereafter he became associated with the Quain & Ramstad Clinic of Bismarck, N. D., in the Department of Internal Medicine. He was an Attending Internist to the Bismarck and St. Alexius Hospitals at Bismarck.

He became a Fellow of the American College of Physicians in 1931 and was certified by the American Board of Internal Medicine in 1937.

Dr. Brandes was a physician with keen diagnostic acumen, sound judgment, and personality and ability that won the respect and admiration of his colleagues, and the confidence and esteem of his patients. He served on the North Dakota State Board of Medical Examiners, and as President of the North Dakota State Medical Association for the year 1939-40. His illness began during the latter part of the time that he was President, and he did not return to the practice of medicine thereafter. Dr. Brandes was always intensely interested in civic matters and, even after the onset of his illness,



assisted in many community and state war-time projects to a remarkable degree. He was a member of the Presbyterian Church, Rotary Club, Masonic Lodge, Scottish Rite Bodies, El Zagal Shrine, and the National Sojourners. He was a member of the Advisory Board of DeMolay.

Dr. Brandes served his home community, his state, and the nation with the greatest of ability and diligence. His interest in his fellow man was reflected by the high esteem in which he was held by all those who had the privilege of knowing him. His fortitude during the long period of his final illness was outstanding. He gave much to the world.

ROBERT B. RADL, M.D., F.A.C.P.,  
Governor for North Dakota

# ANNALS OF INTERNAL MEDICINE

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## THE RESPONSIBILITIES OF THE INTERNIST \*

By DAVID P. BARR, F.A.C.P., *New York, N. Y.*

### FELLOWS OF THE AMERICAN COLLEGE OF PHYSICIANS:

By custom I am permitted as your President to address you on this occasion of the Annual Convocation, and in the few moments at my disposal should like to outline a few of the accomplishments of the College and also to indicate some of the responsibilities which we as Internists may assume in our development. Before doing so, however, I should be neglectful of opportunity if I failed to express to you my profound appreciation of the honor of being allowed during the past year to serve in this high office. Like my distinguished predecessors, I have done my best to advance the purposes of the College. I realize that the little I have accomplished during my term is inadequate evidence of my estimation of the privilege.

The American College of Physicians is the organization of the internists of North America. During the 30 years of its existence it has been responsible for many developments and advances. In its annual and regional meetings it has furnished forum and assembly to consider problems of mutual interest and to foster acquaintance of internists from different districts and different conditions of practice. In its *Annals*, now one of the greater journals of internal medicine, it has been able to publish not only the best of our scientific proceedings but also to make known many of the activities of the College. The American Board of Internal Medicine which was initiated by the College has been useful in establishing standards for practice. Other educational activities of the College have been numerous. Most important perhaps have been the research fellowships for the encouragement and educational opportunity of young men who wish to become internists. The John Phillips Memorial Award has made it possible to honor each year outstandingly significant work in the field of internal medicine or its ancillary sciences and the convocational lectureship has provided for each annual meeting a speaker of national importance.

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\* Presidential Address delivered at the Convocation of the American College of Physicians, Chicago, April 30, 1947.

During the past few years, postgraduate courses of increasing variety have been offered. It is well known to most of you that much of the impetus for this type of instruction in the College came from our former president, Dr. James D. Bruce, whose death last September has saddened us all. Later in the autumn of 1946 it was made known that Dr. Bruce had left a substantial part of his estate to the American College of Physicians and had provided, among other things, for the establishment of a lectureship to honor Dr. Alfred Stengel and for an award of merit for outstanding contribution in Public Health and Preventive Medicine to be known as the James D. Bruce Award in Preventive Medicine, this to be signalized by a medal which the Board of Regents is now having prepared. Dr. Bruce's wise bequest has thus opened the way for further extension of the educational activities of the College and has made possible the beginning of greater emphasis in our meetings on the preventive aspects of disease.

We can take pride in the accomplishments of our organization. It has been more than an instrument for raising the standards of practice and it has gradually assumed an outstanding rôle in the education of internists. In congratulating ourselves, however, we should examine the situation broadly and inquire whether the teaching we are now fostering offers in scope and content the best opportunities for future development.

Consideration of this problem raises again the question which has been posed so many times at these convocations. What, after all, is an internist? You will remember that this was the subject of a most entertaining presidential address by Perry Pepper who concluded that an internist is a creature that cannot be defined. Without attempting to reemphasize the difficulties of definition or to reexamine all the facets of a complex question, it may be assumed that an internist must be both an expert diagnostician and an expert therapist. He must be a master of the method of case-study, a discriminating practitioner of all the technics and skills which may be used to label and classify disease, to relate the symptoms found at the bedside to anatomical deviations, to specifically harmful agents, to the functional capacity of organs, and to chemical abnormalities in the internal environment of the body. He must pride himself on being a scientist at the bedside—on the precise application of his many resources, his physical examination, his discriminating use of the roentgen-ray, his discernment in the selection of chemical and biological tests, and his skill in the interpretation of the electrocardiogram. He must school himself to analyze and synthesize all that he has observed and discovered into a correct and defensible diagnosis of a condition to which he can apply an antibiotic, a hormone, a vitamin, or some other precise remedy. In pursuing this ideal he is in effect extending the dream of Thomas Sydenham that sufficient observation and study will enable the physician to describe and classify all ills and in time to find a specific for each.

These scientific methods employed by internists have been instrumental in the early recognition and satisfactory control of a great number of clinical conditions. They have been helpful in establishing greater freedom from

infection, better nutrition and better health than has been known before. To all of us who use them, however, their limitations are obtrusive. In spite of their increasing complexity and scientific exactitude they may fail to acquaint us with the real problems of the man or woman who is sick. Many times indeed the routine questioning and testing become so elaborate and time-consuming that there is little opportunity for the patient to give or for the internist to hear an unimpeded and uninterrupted account of the illness. It appears that often in the complicated analysis the true goal may be lost. Pope expressed the thought when he said,

"Like following life, through creatures you dissect,  
You lose it the moment you detect."

There is also a question whether anxiety to recognize early organic disease may make one oblivious to the danger of producing invalidism and neurosis, whether chagrin over failure to hear a low-pitched murmur or to feel a palpable spleen is matched by the discomfiture of missing completely the personality of the patient, his hopes and fears, his hates and loves, his obsessions and frustrations, or the indelible imprint which his disease has made on his attitudes and motivations.

If, however, the objectives of the internist are correct diagnosis and optimal treatment these considerations are matters of much more than academic interest, for they are essential to the correct evaluation of symptoms and to the estimate of hypotheses upon which diagnoses and subsequent treatment are based.

The influence which emotions may have on bodily functions has always been realized. To some degree everyone knows the changes that grief, fright, horror, or disgust may accomplish. Great literature is replete with penetrating observations which mirror both the phenomena and their degree.

"I could a tale unfold whose lightest word  
Would harrow up thy soul, freeze thy young blood,  
Make thy two eyes like stars start from their spheres  
Thy knotted and combined locks to stand on end  
Like quills upon the fretful porpentine."

Everyone recognizes the influence of emotion upon the flow of tears, the secretion of sweat, the color of the face, the temperature of the hands. Everyone knows the racing heart of excitement, the gasp of horror, the panting of passion, the polyuria of suspense, and the incontinence of panic.

When one recalls how universally the changes accompanying emotion have been noted, it is surprising that in the past they have been subjected to so little critical analysis. For instance, while it has been known that in those who are embarrassed or resentful the skin may blush, and that in those who are apprehensive or frightened it may become pallid, there has been little curiosity concerning the behavior under similar circumstances of the mucous membranes of the mouth, the nose, the gastric mucosa, the intestinal tract, the pelves of the kidney and the urinary bladder. Nor has there been sufficient

emphasis upon the possibility that while the face might become flushed or pallid without serious consequences, the same might not be true of frequently repeated circulatory changes in body surfaces that were concerned with digestion, assimilation, elimination or other special function. Enthusiasm for chemical and physical investigation of disease has left little time for inquiry concerning the precise effects of the emotions and it is only in recent years that systematic studies along these lines have been attempted.

Such researches, however, have already transformed our concepts of certain diseases, previously regarded as organic and therapeutically susceptible to more or less specific remedies. Most strikingly they have aided us in the understanding and interpretation of gastrointestinal conditions. The classical studies of Harold Wolff and his associates have shown that embarrassment or resentment may cause in the stomach a flushing, a hyperemia and at the same time an increase in secretion of acid; that when these emotions are continuous or often repeated, erosions of the mucosa may occur and that finally actual ulcerations may develop with symptoms indistinguishable from peptic ulcer. Of equal significance were their observations that in the same individual, fear and dread may be accompanied by abnormal pallor of the gastric mucosa with diminution or temporarily complete absence of gastric secretion and with loss of appetite and disgust for food. Similar changes have been seen in the nasal mucous membrane where resentment and embarrassment may produce hyperemia and excessive secretion while fear results in pallor and drying of secretions.

These observations must be regarded as only preliminary and there is little reason to suppose that the responses to emotion of other tissues and organs are less significant. Much evidence is already at hand to indicate that such diverse conditions as asthma, hypertension, thyrotoxicosis, ulcerative colitis and glaucoma have as a part of the symptom complex an emotional component which is significant both etiologically and symptomatically.

In evaluating these studies it must be constantly kept in mind that the reactions to situations cannot be separated sharply into emotional and organic components. In a resentful man the effect of the situation which rouses his resentment will be portrayed in his nose, his stomach, his urinary tract, his posture, and the sour look on his face. The entire organism reacts to environment which it has interpreted as threatening.

Such considerations are of the utmost significance in the daily work of internists. Anatomical and functional organic changes reflecting the play of emotions affect every human being, the sound and strong as well as the sick and weak. Recognizable organic diseases such as diabetes, pernicious anemia, tuberculosis or syphilis do not remove the patient from the category of those who suffer adversely from emotional reactions. Indeed organic disease may exaggerate anxieties, fears and obsessions. On the other hand, freedom from disease and excellent nutrition will not necessarily bring happiness, contentment or freedom from psychological deterioration or emotional disaster.

If we as internists regard the matter soberly, it is apparent that no illness can be correctly formulated or treated unless the patient's environment and his attitudes and reactions to it are taken into account; furthermore that our physical and chemical methods of examination as well as our specifics are inadequate in the care of a vast number of people.

The apparent lack of parallelism between the state of physical well being and emotional and psychological reactions, as well as the inadequacy of our diagnostic and therapeutic resources, appeared most clearly during the stress of war. In spite of incredible hardships and exposures, the well being of our troops as measured by physical means was unprecedented. Under most circumstances there was excellent nutrition and unusual freedom from infection. The majority who became ill were not physically defective or diseased. They came from the ranks of those who were emotionally infirm or maladjusted; of those whose motivation was faulty and who lacked faith and dedication to the purposes of the war. No chemical or physical tests could reveal the depth of their misery, no *specifics* of modern medicine could give them faith, conviction, or courage.

Mature consideration of the situation indicates that this problem which now looms so large in medical practice is but a segment of one of the most cogent realities of our time. Science and scientific methods which can provide useful and comforting things such as freedom from infection, good nutrition, alleviation of pain, and prolongation of life, cannot control fear, or shame, or grief; cannot establish purpose or dedication either for well or suffering human beings; cannot instil faith, hope, love, equanimity, or the other values that make life worth living.

All scientists are in need of Humanism which may be regarded as realization and affirmation of the importance of Man's spiritual values. Physicians whose science is applied to the alleviation of suffering can never dispense with this concept. The internist may remain scientist only so long as his patient has recognizable anatomical and chemical abnormalities which are susceptible to treatment by specific procedures. More often than not, as Alan Gregg has said, ". . . a miraculous moment comes when the doctor becomes the treatment. And it is just there that Science like a relay runner must pass the torch to Humanism."

In medicine as in the world in general, the last few years have been marked by a renewed respect for the humanistic approach. Many factors have contributed to this end. Closer scrutiny of the effects of emotions has pointed the way to a greater appreciation of their clinical significance. The horrors of war and the worldwide misery which has accompanied and followed it have made men realize the limitations of current scientific methods and applications. Contemplation has brought again the realization of the true physician-patient relation which is not scientific but humanistic. The thoughts of a layman of 1850 are relevant. Nathaniel Hawthorne is writing of Roger Chillingworth, the physician of *The Scarlet Letter*, "He deemed it essential, it would seem, to know the man before attempting to do him good.

Whenever there is a heart and an intellect the diseases of the physical frame are tinged with the peculiarities of these. . . . The man of skill, the kind and friendly physician strove to go deep into his patients' bosom, delving among his principles, prying into his recollections, and probing everything with a cautious touch like a treasure seeker in a dark cavern. . . . If he (the physician) possess native sagacity and a nameless something more—let us call it intuition, if he show no intrusive egotism, nor disagreeably prominent characteristics of his own; if he have the power, which must be born with him, to bring his mind into such affinity with his patient's that this last shall unawares have spoken what he imagines himself only to have thought; if such revelations be received without tumult and acknowledged not so often by an uttered sympathy as by silence, an inarticulate breath and here and there a word, to indicate that all is understood; if to these qualifications of confidant be joined the advantages afforded by his recognized character as a physician then at some inevitable moment will the soul of the sufferer be dissolved and flow forth in a dark but transparent dream bringing all its mysteries into the daylight."

Nothing could express more vividly the humanistic approach. No post-war modern with the new light of psychosomatic medicine in his eye could indicate more vividly the limitations of scientific medicine as it is now conceived.

It is deplorable that this most significant aspect of medical practice has been so largely omitted from the training and constructive thought of the internist. In medical schools of the past and even in those of today the emphasis has been upon the recognition and treatment of organic disease or on systemic conditions in which chemical or metabolic defects have been clearly demonstrable. The examinations of the American Board of Internal Medicine have been notably free of any questions concerning emotional factors or life situations in the causation of disease. The programs of the annual and regional meetings of the College have been devoted with few exceptions to physical factors and to pathology which is dependent upon anatomical or chemical deviations.

An attitude is gaining ground among the profession as well as with the laity that if a man has no demonstrable defect and still persists in being ill, he should consult a psychiatrist. Or since psychiatrists are rare and such patients seem to be innumerable, he should perhaps try to find someone who for want of a better term has been called a specialist in psychosomatic medicine, and who has become especially interested in the relationships and interplay of organic and emotional disease.

Such an attitude may have some justification in expediency to meet existing conditions, but can do little toward the final solution of the problem. Psychosomatic medicine is medicine itself. The rôle of humanist cannot be assigned to any one group, whether its members be called psychiatrists, psychosomaticists, or priests. The study of man and his values is at least as much a part of internal medicine as physiology, chemistry, or anatomy.

*Fundamental concepts which involve or modify our understanding of all disease can never be regarded as clinical specialties.*

It must not be expected that we as internists can assume this obligation at once or in full measure. There are many obstacles. We who have received our training in the past have had our attention focused upon the recognition and treatment of organic and mechanical abnormalities. We have been obsessed with the fear of missing the presence of serious or potentially serious anatomical or chemical disease. Intellectually we have been occupied with the relationship of clinical signs and anatomical deviations, with the correction of chemical defects and with the search and application of specifics. We have become burdened with a time-consuming and elaborate ritual to accomplish these purposes. While all of this is praiseworthy it is not enough if in the process we have lost the listening ear and our contacts with patients as people, or if we attempt to make diagnoses and decisions without consideration of personal problems, interpersonal relationships, and life situations in family, occupation and community.

It is by no means implied that all internists are involved in these defects. Osler, Francis Peabody, and many other of our predecessors were great humanists who in being so never lost their respect for science. There are many among us today and not a few of our own number in this College who while applying admirably the methods of science, realize their limitations and in their daily rounds practice a liberal humanism to the great benefit of their patients. The implication is simply that we internists as a group have become perhaps too fascinated with an approach which cannot solve all of the problems of any of our patients or any of the problems of others. Such concentration has too often resulted in a failure to appreciate the realities of the physician-patient relationship.

No originality can be claimed for this thesis. One may hear it better from Plato: ". . . so neither ought you to attempt to cure the body without the soul; and this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole which ought to be studied also; for the part can never be well unless the whole is well. . . . For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body."

In our development as internists and as a College intrusted in no small measure with the education of future physicians, not the least of our obligations should be an attempt to capture a proper balance between scientific study of physical defects and due regard for the emotional and psychological needs of our patients—to promote integration of Science and Humanism in the practice of our art.



# CHRONIC LIVER DISEASE FOLLOWING INFECTIOUS HEPATITIS. I. ABNORMAL CONVALESCENCE FROM INITIAL ATTACK\*

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THE problem of the after-effects of infectious hepatitis is of particular importance at the present time because of the high incidence of this disease during the recent World War. It is now recognized that certain cases of this disease depart from the usual benign course and persist in showing signs and symptoms of liver insufficiency for months or even years following the initial attack. Weakness, fatigue, anorexia, liver tenderness, pain over the liver after exertion, and intolerance to fatty foods have been noted as the most prominent symptoms of this lingering type of hepatitis.<sup>1, 2, 3, 4, 5, 6, 7</sup>

Certain abnormalities in liver function have also been described in these patients. Elevation of the plasma bilirubin has been generally considered the most common aberration. Altschule and Gilligan<sup>8</sup> reported a 25 per cent incidence of hyperbilirubinemia in a group of healthy individuals who had had jaundice one to 29 years previously. Other workers<sup>3, 4, 5, 9</sup> found abnormal excretion of intravenously administered bilirubin, in both symptomatic and asymptomatic cases, following an earlier attack of infectious hepatitis. Barker and associates,<sup>7</sup> in their study of chronic hepatitis in the Mediterranean theatre during World War II, considered bromsulfalein retention the most useful liver function test. Recent reports<sup>10, 11</sup> have emphasized the sensitivity of the thymol turbidity reaction of the serum in detecting persistent liver disease.

The final outcome of cases with lingering hepatitis is not clear. Several workers<sup>12, 13, 14, 15, 16</sup> have described cirrhosis of the liver following infectious hepatitis, but the cases were few in number and usually in an older age group in which other factors, such as poor diet and alcoholism, may have been of importance. Neither the incidence nor the type of cirrhosis following infectious hepatitis is definitely known. A solution to the problem will probably depend upon the close observation and study of a large group of patients for a considerable period of time after their initial attack of infectious hepatitis. This paper deals with the early phase of such a study.

✓ Three hundred and fifty Navy men were admitted to the Hospital of The Rockefeller Institute during the acute stage of infectious hepatitis. Because the men were young and had enjoyed previous good health, this group was

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† Deceased, August 2, 1946.

particularly suited for a study of the chronic aspects of the disease. The diagnosis was easily confirmed in each case by a careful history, physical examination and selected tests of liver function. A minimum of complicating factors was encountered in the group.

The signs and symptoms of liver insufficiency displayed by each patient were carefully followed with special reference to their persistence or recrudescence during convalescence. As a supplement to the clinical observations, numerous laboratory tests were used. It was believed that by such a correlation early abnormalities in the course of the disease could be detected.

After a preliminary study of the results of various tests of liver function,<sup>17</sup> the following determinations were selected as most useful and were carried out at weekly intervals throughout the period of hospitalization:

*Plasma Bilirubin:* Method of Malloy and Evelyn,<sup>18</sup> including one-minute readings introduced by Ducci and Watson.<sup>19</sup>

*Bromsulfalein Retention:* Method of Rosenthal and White<sup>20</sup> modified for use of the Coleman Jr. spectrophotometer. Five mg. of bromsulfalein per kg. of body weight were injected and the per cent retention of the dye determined after 45 minutes.

*Thymol Turbidity:* Method of MacLagen with modification by Shank and Hoagland.<sup>21, 11</sup>

Other tests used at less regular intervals were the following:

*Cholesterol:* Free and total fractions, method of Schoenheimer and Sperry.<sup>22</sup>

*Plasma Protein:* Nesslerization technic from Army Medical Laboratory Manual.<sup>23</sup>

*Hippuric Acid Synthesis:* Method of Quick.<sup>24</sup>

*Cephalin Flocculation:* Modification of Hanger's method.<sup>25</sup>

Dragstedt and Mills<sup>26</sup> found that an elevated plasma bilirubin interfered with the function of the liver involved in the excretion of bromsulfalein. However, in following this group of patients, the determination of bromsulfalein retention was of value even in the presence of clinical icterus. The use of the spectrophotometer eliminated any interference in the laboratory estimation of the bromsulfalein level. In the average uncomplicated case of infectious hepatitis, the plasma bilirubin level and bromsulfalein retention were found to parallel each other closely during the recovery period of the disease (figure 1). Since a divergence in this close relationship was found to be a significant early indication of abnormal convalescence, simultaneous determinations of the two tests were carried out.

Two hundred and ninety of the 350 patients, or 83 per cent, recovered from the acute attack in less than three months, the average period of illness being 56 days. On admission to the hospital, all patients showed definite clinical icterus associated with varying degrees of anorexia, nausea, vomiting, and fever. These symptoms disappeared rapidly after admission and, at the

same time, plasma bilirubin, bromsulfalein retention, and thymol turbidity values showed a sharp fall. Figure 1 represents the normal convalescence observed in a typical case. The criteria for recovery included the disappearance of all symptoms and signs, and the presence of plasma bilirubin levels below 1 mg. per cent and bromsulfalein retention below 5 per cent following a 10-day test period of full activity.

In 60 of the 350 cases, or 17 per cent, recovery did not proceed in the manner just described and hospitalization for longer than three months was required. On the basis of the clinical course and the pattern of serial liver function tests in these cases, it was possible to distinguish the following groups: (1) simple relapse, symptomatic and asymptomatic, with recovery;

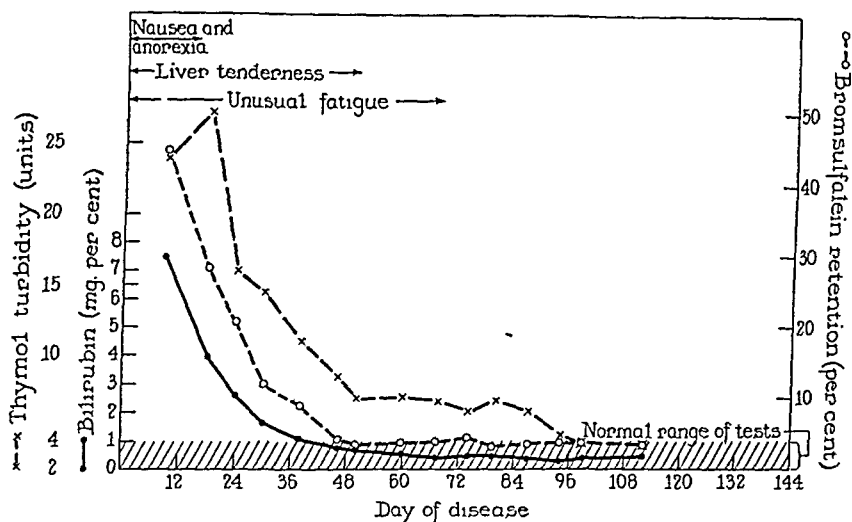


FIG. 1. Serial determinations of plasma bilirubin, bromsulfalein retention and thymol turbidity reaction of the serum in a patient with acute infectious hepatitis showing a normal convalescence.

(2) relapse with transition to chronic hepatitis; (3) chronic hepatitis with persistent bromsulfalein retention; and (4) persistent hyperbilirubinemia, symptomatic and asymptomatic. While such a classification is admittedly artificial, some division was indicated because the patients differed markedly in the type of liver impairment that persisted.

#### GROUP I: SIMPLE RELAPSE WITH RECOVERY

This was the most common group requiring prolonged hospitalization, accounting for 47 of the 60 cases. Only those patients were included who showed an increase in bromsulfalein retention in more than one determination during convalescence. This was always accompanied by an increased thymol turbidity reaction of the serum and usually by a return of clinical symptoms. Figure 2 shows serial determinations in a typical case. Following the cessation of acute symptoms, the plasma bilirubin concentration and the bromsulfalein retention decreased rapidly, just as in the cases showing

a normal convalescence. The serum thymol turbidity values fell more slowly. Approximately one week after admission, the bilirubin level and the bromsulfalein retention had returned to normal; the patient felt well and was anxious to be discharged. After a period of full activity, this patient then developed marked fatigue and an increase in the size of the liver accompanied by tenderness. The return of these clinical indications of liver insufficiency was immediately reflected in an increase in bromsulfalein retention which remained at an abnormal level for the following 10 weeks. The concentration of plasma bilirubin remained normal during the period of relapse. The thymol turbidity values showed a delayed fall at the end of the original acute attack and leveled off at approximately 14 units. Approximately

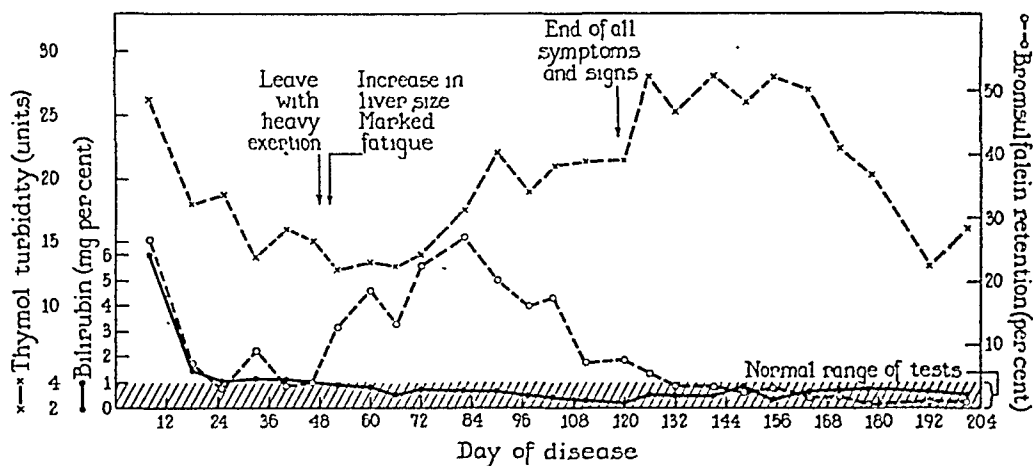


FIG. 2. Serial determinations of plasma bilirubin, bromsulfalein retention, and thymol turbidity reaction of the serum in a patient showing a typical relapse.

three weeks after the onset of the recurrence of symptoms, a definite rise in the values for this test occurred and the elevation persisted for several months.

The other cases in this group were similar to the one discussed above. Tenderness of the liver was the most common physical finding during relapse and was the most useful sign in following the patients clinically. Unusual fatigue, anorexia, pain over the liver, and increase in the size of the liver were frequently encountered. Twenty per cent of the patients in this group showed no clinical signs or symptoms during relapses that were plainly evident through serial determinations of liver function (figure 5).

Measurement of bromsulfalein retention was the most useful single laboratory test for detecting and following both the symptomatic and asymptomatic types of relapse. The results of the test correlated well with the signs and symptoms displayed by each patient, usually showing an increase on the same day that a clinical relapse was noticed. Figure 3 shows graphically the course of a patient who, following a test period of exertion, had an increase in bromsulfalein retention three hours after he developed pain and

tenderness over the liver. This figure also illustrates the value of bromsulfalein retention determinations in the presence of elevated bilirubin levels. Divergence in the usual close parallelism of simultaneous determinations of these two tests gave the first indication of an abnormal convalescence.

Only 35 per cent of these cases in Group I showed a rise in plasma bilirubin levels during relapse. When present, the elevation was very slight (figure 3) and was accompanied by clinical icterus in only one case (figure 4). This test, therefore, was of considerably less value in following relapses than was the determination of bromsulfalein retention.

Results of thymol turbidity measurements reflected every relapse in Group I; the delayed rise and prolonged elevation of values resulting from serial determinations in these cases have been described separately.<sup>11</sup> This test also proved of value in identifying patients that might be candidates for

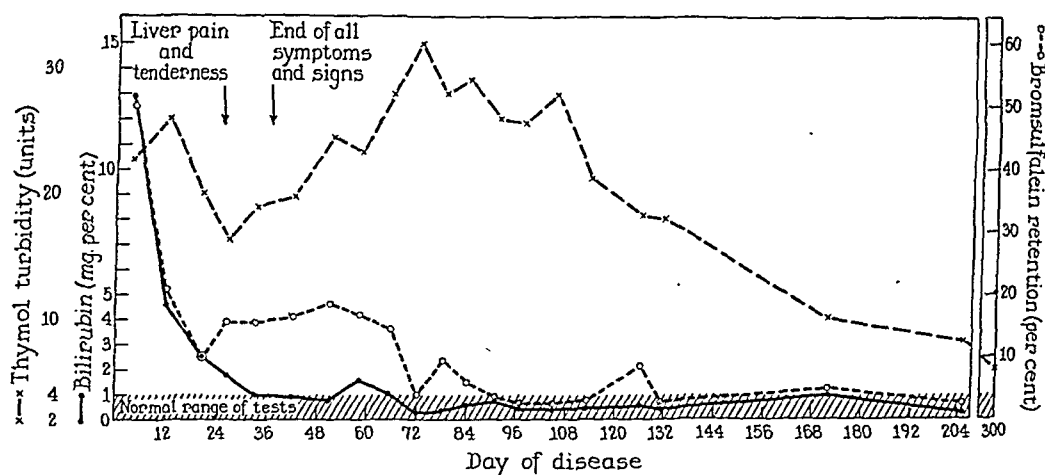


FIG. 3. The detection of a relapse early in convalescence from acute infectious hepatitis. The value of simultaneous serial determinations of plasma bilirubin and bromsulfalein retention in the presence of jaundice is also illustrated.

relapse. In 90 per cent of the cases an elevation above 12 units was found at the time that the relapse began. Such an elevation in a single determination could not be considered significant because of the delayed fall in values for this test in patients showing normal convalescence. However, if such an elevation persisted at a fixed level in several determinations over a period of more than 10 days, the possibility of relapse could be strongly suspected. The patient illustrated in figure 5 showed such a sustained elevation for six weeks prior to relapse.

In one patient of Group I (figure 4) marked clinical symptoms and signs recurred during a relapse precipitated by full activity. Nausea, vomiting, anorexia, abdominal pain, and enlargement and tenderness of the liver were conspicuous clinical features of this recurrence, and the patient was more severely ill than in the initial attack. Bromsulfalein retention and thymol turbidity determinations reached extremely high values. The bilirubin level also rose and the patient developed definite clinical icterus.

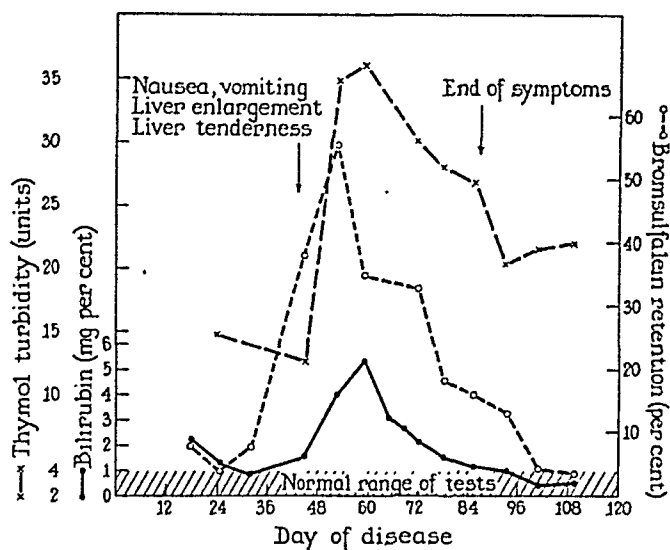


FIG. 4. Severe relapse of acute infectious hepatitis with recurrent icterus.

Exertion has been mentioned as a factor in the precipitation of relapses. Thirty-eight of the 47 cases described above suffered relapses during a test leave period when full activity was resumed for the first time. A typical case is illustrated in figure 2. While on leave, the patient took a long train trip. The following morning he was very tired and unable to eat. These symptoms persisted and, on his return to the hospital three days later, it was found that his bromsulfalein retention had increased. It then remained abnormal for approximately 10 weeks. In nine of the 47 cases no definite inciting factors could be discovered; in fact, two patients developed a relapse while on complete bed rest. One patient (figure 5) was kept in bed, although he felt perfectly well, in order to facilitate the return to normal values of the

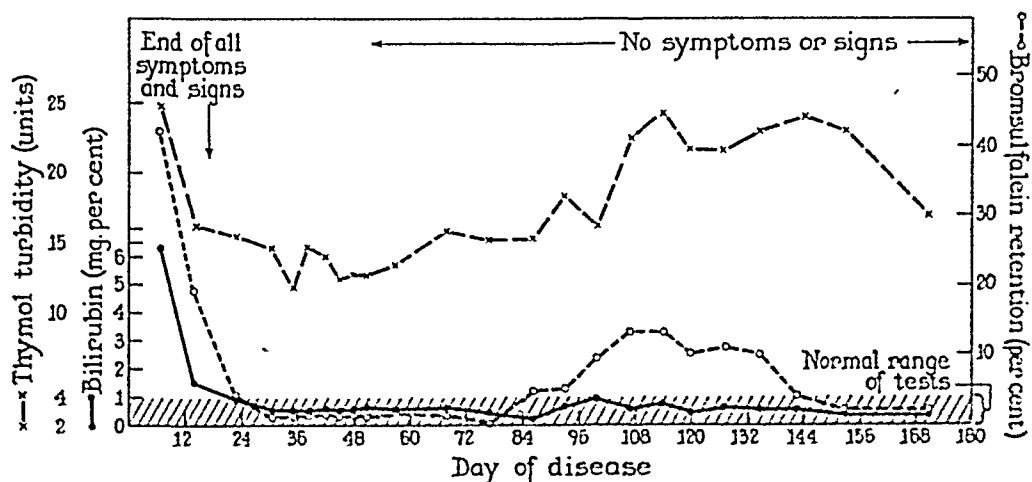


FIG. 5. Asymptomatic relapse late in convalescence from acute infectious hepatitis illustrating (1) relapse during bed rest therapy, (2) the significance of a sustained elevation of the thymol turbidity test during convalescence.

thymol turbidity test. On the eighty-seventh day of his illness he developed a slight increase in bromsulfalein retention and then showed laboratory evidence of a relapse for a six-week period despite continued bed rest. At no time during this period did the patient develop any symptoms or signs of

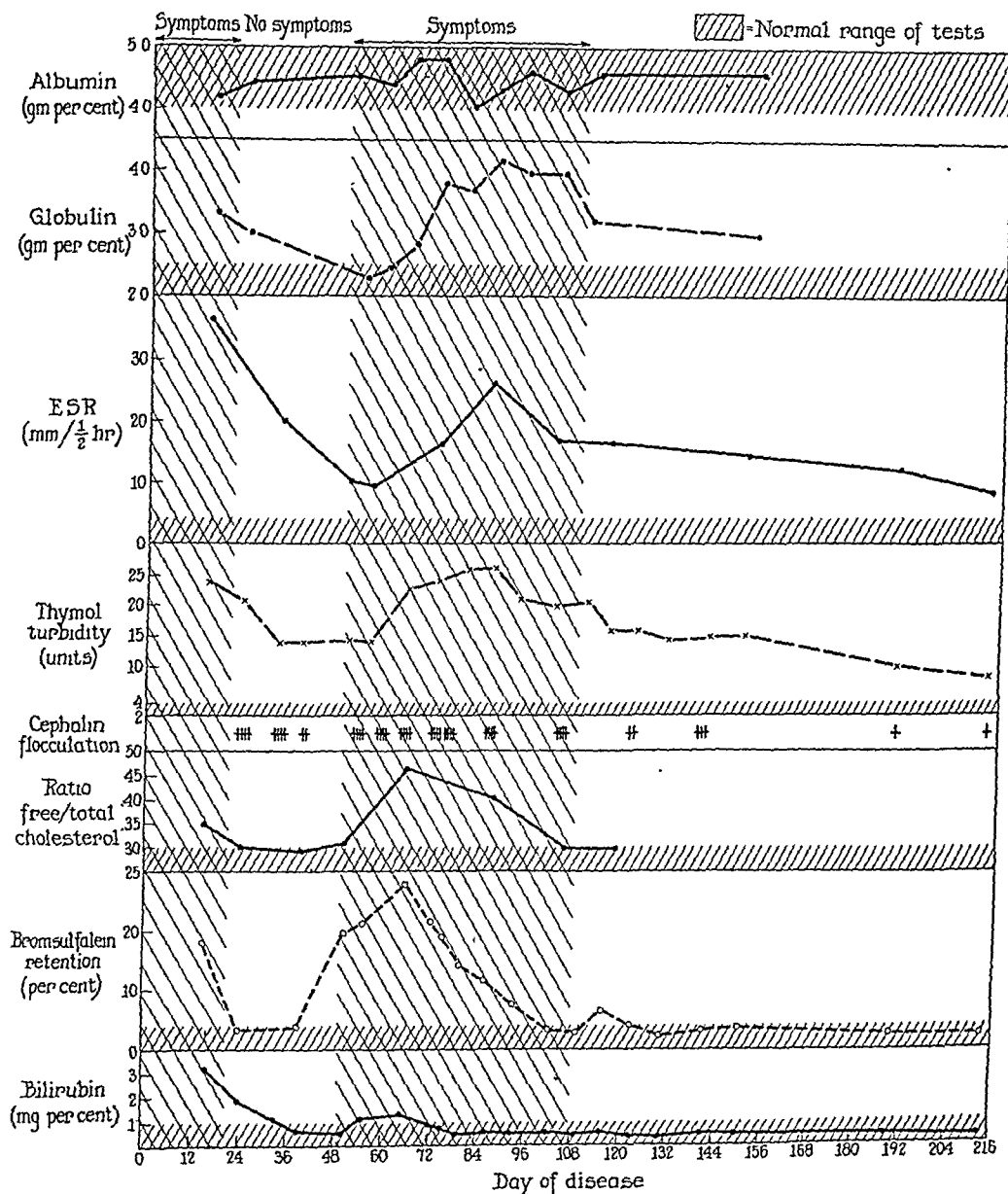


FIG. 6. Serial determinations of multiple tests of liver function in a patient showing a typical relapse of infectious hepatitis.

liver insufficiency. These two cases show definitely that factors other than exertion may be concerned in the development of relapses.

Study of the mild relapses offered an unusual opportunity for comparative evaluation of various liver function tests (figure 6). Results of the plasma

bilirubin level, the bromsulfalein retention test and the thymol turbidity reaction of the serum have been described. Other tests of liver function also reflected the state of relapse. The ratio of free to total cholesterol was found to be a very sensitive test, and serial determinations produced curves closely paralleling those of bromsulfalein retention. This test was not used regularly because of the technical difficulties in making accurate determinations. Serial hippuric acid synthesis measurements were also found to reflect some of the relapses in a manner similar to those of bromsulfalein retention. However, during very mild relapses there was no change, indicating that under these conditions hippuric acid synthesis is not so sensitive a test as is bromsulfalein retention.

The cephalin flocculation test was used in some of the cases (figure 6). The values roughly paralleled those of the thymol turbidity reaction, but, because quantitative measurements were more difficult, serial determinations of the cephalin flocculation test did not produce curves that could be clearly interpreted. The plasma albumin level was altered very little during relapse. However, the total plasma globulin showed a delayed elevation and roughly paralleled the thymol turbidity reaction of the serum. The erythrocyte sedimentation rate, although not a liver function test, showed marked alterations during relapse and serial determinations closely followed the pattern of the globulins. The protein changes following relapse will be described in more detail in a separate communication.

Patients who had transitory elevations in bromsulfalein retention and thymol turbidity values were not included in the group with relapses. However, it must be emphasized that all degrees of reversal may occur during convalescence from infectious hepatitis, ranging from mild asymptomatic changes, through the definite relapse patterns discussed, to the severe relapses that occasionally end in death.<sup>6</sup>

As soon as the onset of a relapse was detected by an increase in bromsulfalein retention, the patient was returned to complete bed rest until the results of this test reached a normal level. All 47 of the patients in the first group showed complete recovery from their relapses and were able to tolerate a second period of full activity without developing further trouble.

## GROUP II: RELAPSE WITH TRANSITION TO CHRONIC HEPATITIS

Two patients suffered relapses that began in a manner similar to those described in Group I. However, these men did not recover entirely, but showed persistent slight aberrations in bromsulfalein retention and thymol reactivity of the serum for more than 12 months. In addition, both of these patients complained of fatigability and occasional episodes of pain and tenderness over the liver throughout this period. Figure 7 shows the persistent abnormal values of tests of liver function in one of the patients. Somewhat less significance can be applied to the persistent elevation of the thymol turbidity values in these two cases because in other patients showing



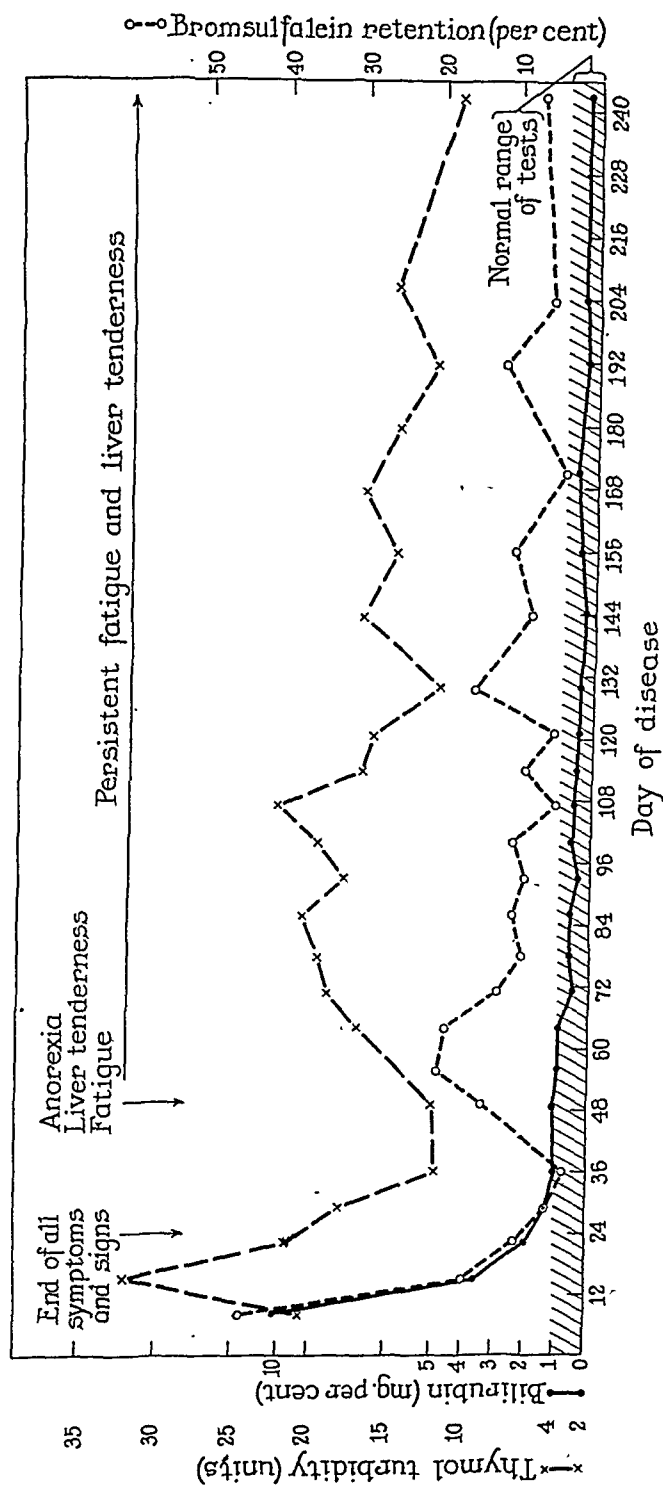


FIG. 7. Serial liver function determinations in a patient showing chronic hepatitis following a relapse.

complete recovery from relapse the values for this test remained elevated for many months. The slight but definite increase in bromsulfalein retention, however, correlated well with persistent symptoms of slight disturbance in the function of the liver. Both of these patients showed a persistent increase in the globulin of the serum, but the albumin level remained normal. No spider angiomas were found. The men are still being followed carefully and appear to be showing slight improvement although fatigability and liver tenderness persist.

### GROUP III: CHRONIC HEPATITIS WITH PERSISTENT BROMSULFALEIN RETENTION

This group included four of the 60 patients showing abnormal convalescence, and was characterized by elevation of bromsulfalein retention with persistent clinical symptoms and signs of disturbance in the liver for more than 12 months. Since these patients showed little evidence of improvement during the usual period of convalescence, they could not be classified with those in the group with relapses. Figure 8 illustrates a typical case. The symptoms of the acute attack in this instance were mild and there followed rapid subsidence of jaundice and gastrointestinal distress. The liver, however, remained slightly enlarged and definitely tender and showed no evidence of improvement during the entire 12 months that the patient was in the hospital. Tenderness of the liver manifested itself in several ways: (1) light palpation of the liver elicited slight pain which often persisted for as long as two days; (2) sleeping on the right side caused local discomfort; (3) pain and tenderness occurred over the left lobe of the liver following large meals to such an extent that the patient hesitated to eat freely. In addition, this patient showed marked fatigue after mild exertion, and was unfit for work. He is still being followed after 18 months and the undue fatigue and tenderness of the liver persist, although there is some improvement in his general condition. Several new crops of spider angiomas developed during the year of observation. There was a persistent marked increase in bromsulfalein retention as shown in figure 8. Values for the thymol turbidity test were only slightly elevated but remained abnormal over the entire period of hospitalization. Slight, but definite, diminution of the albumin of the plasma was also present associated with slight elevation of the globulin, and the A/G ratio averaged 1.1. The cephalin flocculation test never became positive.

The remaining three cases of the group were similar to the one described. They were characterized by persistent liver tenderness, unusual fatigue and increased bromsulfalein retention. The thymol turbidity values were only slightly elevated in two of the cases, while in one they were normal in the presence of severe clinical symptoms. The thymol turbidity test was of little value in following these men and did not give the high values seen in the group of patients with relapses. In all but one of the patients, new spider

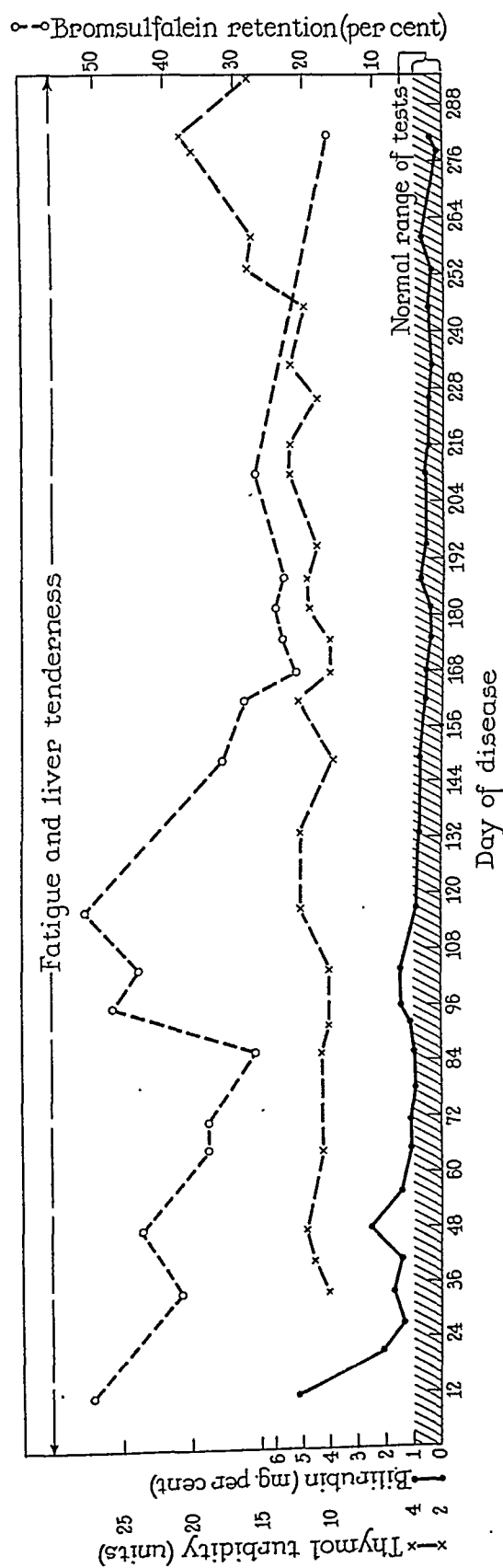


FIG. 8. Serial liver function determinations in a patient showing severe chronic hepatitis following an acute attack of infectious hepatitis.

angiomata developed more than six months after the acute attack of infectious hepatitis. The four patients in this group showed the most marked symptoms and signs of persisting liver insufficiency of the entire series. These findings correlated well with the increased bromsulfalein retention which was also more marked than in any other group.

#### GROUP IV: PERSISTENT HYPERBILIRUBINEMIA

Seven of the 60 patients showing an abnormal convalescence required prolonged hospitalization because of persistent elevation of plasma bilirubin values and were finally discharged despite an elevation above 1 mg. per cent. Figure 9 illustrates a typical case from this group. The acute phase of

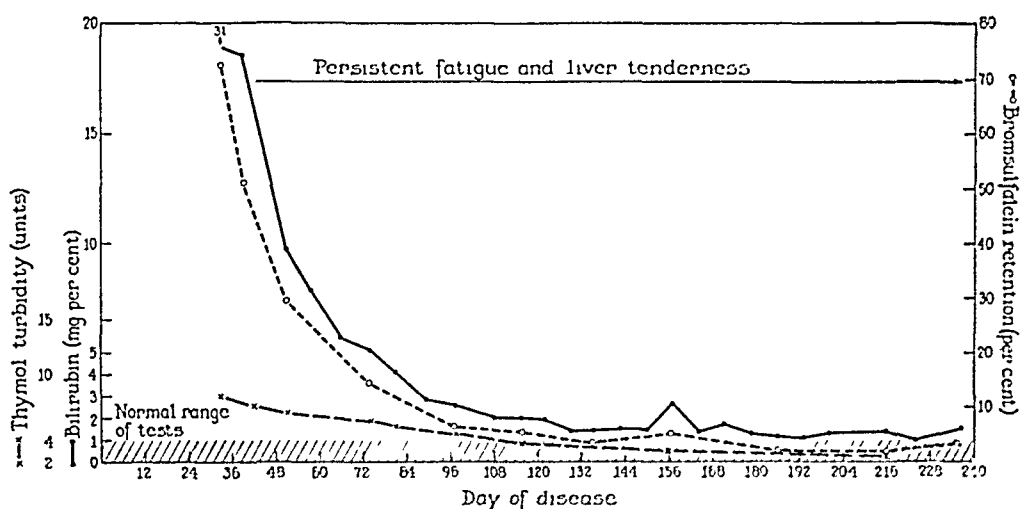


FIG. 9. Persistent hyperbilirubinemia following an acute attack of infectious hepatitis.

hepatitis in this patient was severe and was characterized by extremely high plasma bilirubin values. These values fell to normal more slowly than in the average uncomplicated case, finally leveling off at approximately 2 mg. per cent, despite the fact that the patient was kept at complete bed rest for three months. Hyperbilirubinemia persisted throughout the 200 days that the patient was in the hospital. The bromsulfalein retention and thymol turbidity determinations gave no indication of an abnormal convalescence. The cephalin flocculation test became negative at the end of the acute attack. In addition to the elevation in plasma bilirubin, this patient showed persistent fatigue throughout the period of observation. At the time of discharge he was unable to walk more than two blocks without feeling exhausted. The only other finding that was noted was an occasional episode of slight tenderness of the liver. Five other patients showed a similar course and were discharged after a long period of hospitalization with bilirubin values above 1 mg. per cent. They differed only in that the clinical picture initially was considerably milder with less intense icterus. The bromsulfalein retention

and the thymol turbidity tests gave no indication of an abnormal course. In these men the excretion of bilirubin by the liver appeared to be selectively impaired.

The seventh case in this group (figure 10), in addition to showing persistent hyperbilirubinemia, suffered a relapse during convalescence, characterized by transitory mild symptoms and a rise in bromsulfalein retention and thymol turbidity values. Throughout the entire course of this patient's

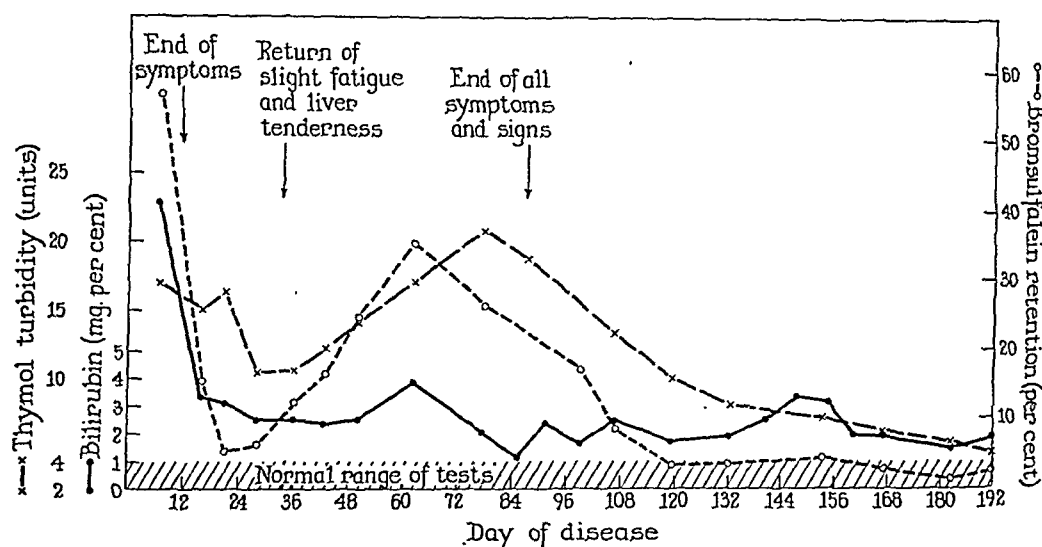


FIG. 10. Relapse during acute infectious hepatitis with persistent hyperbilirubinemia.

illness the bilirubin level stayed at approximately 3 mg. per cent. The mild symptoms during the relapse disappeared and the patient was discharged with an asymptomatic hyperbilirubinemia after being hospitalized for 186 days. This case suggests some relationship between this group and Group I. The persistent elevation of the plasma bilirubin in Group IV was mainly in the indirect-reacting component, while the 1-minute or direct-reacting portion fell to normal at the end of the acute attack (table 1). It is of significance

TABLE I

Relative Amounts of the Direct and Indirect Bilirubin Components at Various Periods during the Illness of the Patient Illustrated in Figure 9

Day of Illness	1 Min. or Direct Reacting Bilirubin mg. %	30 Min. or Total Bilirubin mg. %	Indirect Reacting Bilirubin % of total
34th	14	31	55
58th	4.1	8.0	19
80th	1.9	4.0	52
120th	1.1	2.5	56
135th	0.1	1.5	93
172th	0.2	1.8	89
200th	0.1	1.3	92
236th	0.1	1.6	94

that the slight persistent elevation of the plasma bilirubin was associated with symptoms of liver insufficiency in three of the seven cases.

### DISCUSSION

Relapse was by far the most common cause of prolonged hospitalization in the group of 60 patients discussed. This usually occurred following the first period of full activity. Many other patients, not included in the group, were found to develop transitory changes in liver function tests following such activity. It was evident that most patients with infectious hepatitis were very susceptible to further injury of the liver during the convalescent period despite the fact that they no longer showed clinical signs or symptoms of the disease and had normal values for plasma bilirubin and bromsulfalein retention. It is undoubtedly important that these patients be followed carefully with tests of liver function during the period of resumption of their activity. Occasionally, it was possible to anticipate relapse because of sustained elevation of the thymol turbidity test at a fixed level during convalescence. However, the value of this test in predicting relapses was somewhat lessened by the fact that at times it fell to normal slowly even in patients who showed a normal convalescence.

In the average case, symptoms and signs of liver insufficiency were very mild during relapse; 20 per cent, or 10, of the 49 cases in Group I showed no clinical signs or symptoms. Clinical jaundice was present in only one case and plasma bilirubin elevation was detected in only one third of the patients. Most of the relapses, therefore, might have gone undetected. It was only by means of serial determinations of bromsulfalein retention that they were clearly recognized. Relapses have been described in infectious hepatitis which were usually apparent only because of a return of jaundice and clinical signs and symptoms of the disease. The importance of the bromsulfalein test in detecting the relapses that occur without jaundice has not been sufficiently emphasized. This test became positive almost immediately after the onset of a relapse and, as a result, these patients could be returned immediately to bed rest.

The importance of bed rest in preventing chronic liver disease has never been clearly established. However, since activity was the usual initiator of a relapse, it is reasonable to believe that limitation of activity might be of considerable importance after the relapse has begun. Fishman<sup>6</sup> described fatal relapses in two men which occurred under combat conditions. These relapses corresponded in time to those in Group I of the present study. The severity of the relapses may very well have resulted from the fact that the two men were forced to continue activity until marked jaundice appeared. Two ex-service men, who are now being studied at this hospital, present the clinical picture of severe cirrhosis of the liver following attacks of infectious hepatitis four years ago. Both men developed relapses with return of jaundice approximately two months after the initial attack. They continued

activity despite these changes because of wartime duties. The jaundice that returned during the relapse states never disappeared and both patients have gradually failed. In the present series, all but two of the 49 patients who suffered relapses recovered entirely in less than six months' time. It seems possible that the early detection of the relapses and immediate restriction of activity may have been partially responsible for the subsequent benign course in the majority of the patients.

The question as to whether the relapses were caused by a reactivation of the virus of infectious hepatitis has not been answered. Neefe<sup>27</sup> attempted to transmit the disease to human volunteers by means of material obtained from patients with a lingering hepatitis during a period that corresponded to the time of the relapses described in the present paper. The results were not conclusive. Further work is necessary to elucidate this important question.

In addition to those showing relapses, four patients (Group III) were described who showed marked symptoms of fatigue and liver tenderness continually for more than 12 months. These patients apparently never recovered completely from their initial attack. Bromsulfalein retention remained at a high level throughout the period of observation. The possibility of the development of cirrhosis must be considered in these cases. Two of these patients now show alteration of A/G ratio by virtue of a fall in albumin and elevation of globulin, but there is no evidence of edema or ascites. Several new crops of spider angiomas have appeared in three patients of the group. The prognosis is undoubtedly more grave in these patients who showed continued bromsulfalein retention for more than 12 months than in those in Group I who showed bromsulfalein retention solely during the course of a relapse, even though the values may have reached higher levels in the latter group.

The fourth group of patients, seven in number, showing an abnormal convalescence, was characterized by a selective abnormality in bilirubin metabolism. All other tests of liver function were consistently negative. These included determinations of urine bilirubin, bromsulfalein retention, the thymol turbidity reaction, the thymol flocculation reaction,<sup>10</sup> the cephalin flocculation reaction, the ratio of free to total cholesterol, and the plasma proteins. Three of the patients had persistent symptoms of fatigue and tenderness of the liver associated with elevated plasma bilirubin for more than 12 months after the initial attack. The remaining patients were without symptoms despite persistent mild hyperbilirubinemia. The elevation in plasma bilirubin in all the patients was usually entirely of the indirect reacting type. They presented the picture of a hemolytic jaundice without other evidences of red blood cell destruction such as anemia, increased fragility of the red cells and splenomegaly. This group is definitely different from the other cases discussed.

As has been pointed out, liver function tests often showed evidence of an

abnormal convalescence in the absence of other findings. However, it should be emphasized that in all cases in which there were clinical symptoms and signs of relapse or of a lingering hepatitis, there were also accompanying aberrations in at least one of the three main liver function tests mentioned.

The eventual outcome of the 60 patients in the four groups showing abnormal convalescence is uncertain. At present, it can be stated that all but eight recovered sufficiently in less than one year to tolerate a test period of full activity without symptoms or signs of liver insufficiency. The eight who did not recover in this manner are still being observed carefully. The factors responsible for such a prolonged course are not clear. The severity of the initial attack had no relation to the incidence of relapse or prolonged convalescence. Four of the eight had comparatively mild acute attacks of infectious hepatitis. The only tangible factor was age. The eight patients referred to above averaged 31 years of age, while the average age of the entire group of 350 patients was 24. This may be an important difference in determining ability to recover and, in light of these data, it is undoubtedly wise to manage patients over 30 years of age with acute infectious hepatitis more conservatively than those in younger groups.

This study has dealt only with those patients showing abnormal convalescence. The other members of the group of 350 patients who showed a normal convalescence and who were able to tolerate a test period of full activity without difficulty should also be observed for development of signs of hepatic insufficiency at some future time. Studies on the entire group of patients must be continued for many years in order to answer the question of the development of cirrhosis. The patients who experienced the early complications described in this paper should be observed with special care.

### SUMMARY

1. Three hundred and fifty patients with acute infectious hepatitis were studied.

2. Sixty, or 17 per cent, showed abnormal convalescence.

3. Of the 60, 47 showed a simple relapse with recovery; two, relapse with transition to chronic hepatitis; four, chronic hepatitis with persistent bromsulfalein retention; and seven, persistent hyperbilirubinemia.

4. A comparative evaluation of certain liver function tests used in following the patients with abnormal convalescence was made.

5. Determination of bromsulfalein retention was found to be of particular value in detecting relapses.

6. The importance of the combined use of the plasma bilirubin level, the bromsulfalein retention and the thymol turbidity reaction of the serum for following the various types of persistent impairment of the liver, was emphasized.

7. Eight patients, or 2.3 per cent, did not recover completely after more than one year's time.



## BIBLIOGRAPHY

1. POLACK, E.: Chronic hepatitis in young persons, with or without intermittent jaundice, *Acta med. Scandinav.*, 1937, xciii, 614-621.
2. ABRAMSON, L.: On hepatitis chronica in younger persons, *Acta med. Scandinav.*, 1941, cviii, 561-567.
3. KORNBERG, A.: Latent liver disease in persons recovered from catarrhal jaundice and in otherwise normal medical students as revealed by the bilirubin excretion test, *Jr. Clin. Invest.*, 1942, xxi, 299-308.
4. KALK, H.: Klinische Untersuchungen über die Frage des latenten Leberschadens, *Deutsch. med. Wchnschr.*, 1932, lviii, 1078-1080.
5. MJASSNIKOV, A. L.: Über akute Hepatitis mit Ascites und über den Übergang der akuten Hepatitis in eine chronische (Cirrhose), *Klin. Wchnschr.*, 1931, x, 836-839.
6. FISHMAN, A. P.: Persistent hepatitis in patients returning from overseas, *Bull. U. S. Army Med. Dept.*, 1945, iv, 457-462.
7. BARKER, M. H., CAPPS, R. B., and ALLEN, R. B.: Chronic hepatitis in the Mediterranean theater, *Jr. Am. Med. Assoc.*, 1945, cxxix, 653-659.
8. ALTSCHULE, M. D., and GILLIGAN, D. R.: Chronic latent hepatitis following catarrhal jaundice, *New England Jr. Med.*, 1944, ccxxxi, 315-317.
9. SOFFER, L. J., and PAULSON, M.: Residual hepatic damage in catarrhal jaundice as determined by the bilirubin excretion test, *Arch. Int. Med.*, 1934, liii, 809-813.
10. NEEFE, J. R.: Results of hepatic tests in chronic hepatitis without jaundice, *Gastroenterology*, 1946, vii, 1-19.
11. KUNKEL, H. G., and HOAGLAND, C. L.: Persistence of elevated values for the thymol turbidity test following infectious hepatitis, *Proc. Soc. Exper. Biol. and Med.*, 1946, lxii, 258-261.
12. RENNIE, J. B.: Infective hepatitis, *Am. Jr. Med. Sci.*, 1945, ccx, 18-29.
13. EPPINGER, H.: *Die Leberkrankheiten*, 1937, Vienna, Julius Springer.
14. KRARUP, N. B., and ROHOLM, K.: The development of cirrhosis of the liver after acute hepatitis, elucidated by aspiration biopsy, *Acta med. Scandinav.*, 1941, cviii, 306-331.
15. CULLINAN, E. R.: Idiopathic jaundice, often recurrent, associated with subacute necrosis of the liver, *St. Bartholomew's Hosp. Rep.*, 1936, lxix, 55-142.
16. WATSON, C. J., and HOFFBAUER, F. W.: The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver, *Ann. Int. Med.*, 1946, xxv, 195-227.
17. SHANK, R. E., BINKLEY, F., and HOAGLAND, C. L.: A study of the changes produced in components of plasma and in various tests of liver function in acute infectious hepatitis. (To be published.)
18. MALLOY, H. T., and EVELYN, K. A.: The determination of bilirubin with the photoelectric colorimeter, *Jr. Biol. Chem.*, 1937, cxix, 481-490.
19. DUCCI, H., and WATSON, C. J.: The quantitative determination of the serum bilirubin with special reference to the prompt-reacting and the chloroform-soluble types, *Jr. Lab. and Clin. Med.*, 1945, xxx, 293-300.
20. ROSENTHAL, S. M., and WHITE, E. C.: Clinical application of the bromsulphalein test for hepatic function, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 1112-1114.
21. SHANK, R. E., and HOAGLAND, C. L.: A modified method for the quantitative determination of the thymol turbidity reaction of serum, *Jr. Biol. Chem.*, 1946, clxii, 133-138.
22. SCHOENHEIMER, R., and SPERRY, W. M.: A micromethod for the determination of free and combined cholesterol, *Jr. Biol. Chem.*, 1934, cvi, 745-760.
23. ARCHIBALD, R. M.: *Army Medical Laboratory Manual* (to be published).
24. QUICK, A. J.: The clinical application of the hippuric acid and the prothrombin tests, *Am. Jr. Clin. Path.*, 1940, x, 222-233.

25. HANGER, F. M.: The flocculation of cephalin-cholesterol emulsions by pathological sera, *Trans. Assoc. Am. Phys.*, 1938, liii, 148-151.
26. DRAGSTEDT, C. A., and MILLS, M. A.: Bilirubinemia and bromsulphalein retention, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 467-468.
27. NEEFE, J. R., STOKES, J., JR., GARBER, R. S., and GELLIS, S. S.: Studies on the relation of the hepatitis virus to persistent symptoms, disability, and hepatic disturbance following acute infectious hepatitis, *Jr. Clin. Invest.*, 1947, xxvi, 329-338.

# ARTERIALIZATION OF INTERNAL JUGULAR BLOOD DURING HYPERVENTILATION AS AN AID IN THE DIAGNOSIS OF INTRACRANIAL VASCULAR TUMORS \*

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THE diagnosis of intracranial vascular tumors is important because treatment is, as a rule, nonsurgical; often roentgenological treatment is the procedure of choice. In the diagnosis of vascular tumors certain criteria have been useful: (a) Roentgenologic evidence of calcification of the vessel walls; (b) Roentgenologic evidence of a vascular pattern from erosion of the inner table of the skull; (c) Pneumoencephalographic evidence of a space-consuming lesion as indicated by depression of the ventricle with, however, an apparent increase in the depth of the subarachnoid spaces over the convexity; (d) The presence of a bruit; (e) The presence of angiomas in the fundi (i.e., with cerebellar hemangioma of the Lindau type) or of angiomas in the pancreas and kidneys; (f) The presence of morphological changes in the cerebral vessels as demonstrated by intracranial angiography. Diagnosis, however, is still a very difficult problem, and the addition of any further diagnostic procedures would be helpful in avoiding unnecessary operations.

In the course of study of 69 samples of internal jugular blood taken before and during hyperventilation in persons without vascular tumors, it was found that the usual reaction was for the oxygen content to fall during hyperventilation. In a small percentage of the cases the oxygen content remained unchanged or rose slightly. Evidence is available that during hyperventilation cerebral blood flow decreases while extracranial blood flow to the head usually increases, and the composition of the internal jugular blood reflects, in part, the cerebral vasoconstriction plus contributions from extracranial sources through cranial anastomoses.<sup>1</sup>

The presence of a vascular tumor might result in shunting of blood through the vascular anomaly during the cerebral vasoconstriction associated with hyperventilation, hence leading to increased arterialization of the internal jugular blood. If this shunt were of any size, this would be revealed by rising O<sub>2</sub> and falling CO<sub>2</sub> contents of the jugular blood, in contrast to the usual response. Opportunity to test this point presented itself when a patient with a proved intracranial vascular tumor was studied. The vascular character of the tumor in this case was not diagnosed preoperatively. Of the above criteria, only the pneumoencephalographic findings of depression

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of a lateral ventricle were present preoperatively and this suggested merely the presence of a space-consuming lesion.

#### CASE REPORT

The patient was a 22 year old single white man with a four and one-half year history of attacks characterized by right-sided numbness beginning in the tips of the fingers and progressing to the hand, arm, right half of the face and tongue, then to the right half of the chest and abdomen and finally, to the right leg and foot. This was followed by right hemiparesis, which in the earlier attacks lasted about 24 hours,



FIG. 1. Photograph of hemangioma taken at time of operation.

but in the last few months had become permanent. These attacks occurred two to three times a week. Significant physical findings were weakness of the right lower face and right extremities with some clumsiness of the fingers and toes in performing fine movements and some spasticity of the right leg when walking. There was slight drift of the extended right arm. No bruit was heard on auscultation of the head.

Pneumoencephalogram revealed some depression of the roof of the left lateral ventricle in portions three and four and the first part of six. The subarachnoid spaces showed slightly decreased filling in the parietal regions bilaterally.

A left parietal osteoplastic craniotomy was performed exposing a wide-spread vascular malformation in the left frontoparietal region, the extent of which is evident in the accompanying photograph (figure 1). Included in this was a large main

vessel 3 to 4 mm. in diameter with occasional tributaries, and several accessory vessels of smaller size. A deep groove was found in the bone overlying the large vessel. (In retrospect this groove was evident in the roentgenogram.) The blood in all of the major vessels of the tumor seemed arterial in appearance. Neither compression of the large vessel above described, nor compression of each of the main vessels of the neck seemed to alter blood flow through the tumor. No thrill or bruit was elicited at this time, but one week postoperatively a loud bruit was heard for the first time over the entire head, loudest on the left.

*Bilateral Internal Jugular Vein Puncture.* Bilateral internal jugular vein puncture was carried out six months post-operatively. After procaine infiltration of the overlying skin and subcutaneous tissues, the internal jugular veins were punctured as close to their point of emergence from the jugular foramen as possible by inserting the needle between the mastoid process and the angle of the mandible and directing it upward.<sup>2</sup> Blood samples were obtained simultaneously from both veins before and again at one and three minute intervals after beginning vigorous hyperventilation. Indwelling obturated needles were used. The blood samples were collected in tight-fitting syringes containing 1 to 2 c.c. of mineral oil, and stored in mercury vessels. Samples were analyzed for oxygen and carbon dioxide by the Van Slyke manometric

TABLE I  
Simultaneous Left and Right Internal Jugular Blood During Hyperventilation

Time of Hyperventilation	Sample	Whole Blood Oxygen Vol. %	Oxygen Saturation %	Whole Blood CO <sub>2</sub> Vol. %	pCO <sub>2</sub> mm.Hg	pH
Control	Left	17.2	79	53.5	50.0	7.34
	Right	18.8	86	52.5	48.0	7.35
1'15"	Left	19.1	87	41.8	26.0	7.55
	Right	19.8	91	41.2	25.0	7.57
3'15"	Left	19.3	90	42.0	25.5	7.59
	Right	20.5	95	41.3	24.5	7.60

technic; pH was determined with a MacInnis glass electrode. From the data on pH, carbon dioxide content and hematocrit the carbon dioxide tension was calculated by the Henderson-Hasselbalch formula.

*Results.* The results of the studies carried out are listed in table 1. It will be noted that the prehyperventilation values for oxygen content and saturation were high, and that during hyperventilation these values approached those of arterial blood (saturation 90 to 95 per cent). The carbon dioxide content fell from 53.5 to 42.0 volumes per cent on the left and from 52.5 to 41.3 volumes per cent on the right. The pH rose from 7.34 to 7.59.

## DISCUSSION

The notable finding is the marked rise in oxygen content and oxygen saturation of the internal jugular blood during hyperventilation so that it closely approaches the composition of arterial blood. The changes in carbon dioxide content and pH are consistent but less striking, so that for diagnostic purposes determination of oxygen saturation alone gives the necessary information. The results may be compared with analyses of 69 internal jugular blood specimens from normal medical students and coöperative

patients who had no cerebral vascular tumors.<sup>1</sup> There were no instances among this group in which a comparable rise in oxygen saturation during hyperventilation was noted. In 60 of the 69 analyses the oxygen saturation fell to a mean average of 37 per cent (range 14 to 58 per cent). We have designated this pattern I.<sup>1</sup> In 9 of the 69 analyses the oxygen saturation remained unchanged or rose slightly (average, 65 per cent, range 50 to 76 per cent). We have designated this pattern II. Evidence has been presented that pattern II represents examples of internal jugular blood to which a high proportion of extracranial blood has been added.<sup>1</sup> In this relatively large experience we have never encountered in other subjects an oxygen saturation during hyperventilation as high as that noted in our patient with the intracerebral vascular tumor. Even the oxygen saturation of external jugular blood during hyperventilation in two patients (values of 77 per cent and 87 per cent respectively) did not exceed that noted in our patient. This would suggest that during hyperventilation there is greatly increased shunting of blood through the vascular tumor.

The prehyperventilation oxygen saturations in our patient were also high (79 to 86 per cent). In the control subjects the prehyperventilation oxygen saturations averaged 56 per cent with a range of 34 to 69 per cent in the 60 examples of pattern I, and averaged 63 per cent with a range of 51 to 74 per cent in the 9 examples of pattern II. As compared to control subjects the prehyperventilation values in the patient are suggestive of the diagnosis but not as decisive as the values during hyperventilation. Occasionally in patients with severe encephalopathy and coma comparatively high venous oxygen saturation may be noted in the presence of reduced cerebral metabolism. Thus among 18 patients with encephalopathy from various causes one was found with an internal jugular oxygen saturation of 84 per cent. This patient had malignant hypertension and uremia and was in coma at the time of the examination.<sup>3</sup> Obviously diffuse encephalopathy is not apt to present an important problem in the differential diagnosis of intracerebral vascular tumors except perhaps in instances in which such tumors have recently been complicated by intracerebral or subarachnoid bleeding.

Internal jugular punctures cannot be expected to be of help in locating the tumor because of the many anatomic variations in the great venous sinuses.<sup>4</sup> Although the vascular anomaly in our patient was on the left the oxygen saturation was higher on the right suggesting that a greater proportion of the venous drainage of this tumor was directed toward the right lateral sinus. Anatomically it is conceivable that in some cases the venous drainage of the tumor would be to one side, not necessarily the same side. Hence, the finding of normal blood on one side does not rule out vascular tumor. For ordinary purposes, then, it is probably best to study blood from the internal jugular vein on one side and if this is normal or equivocal, to examine the opposite side.

Technically the procedure is simple and without risk. It is much less formidable than the injection of opaque materials into the internal carotid

artery. In many hundred internal jugular vein punctures performed by us in the past six years we have never encountered any serious accident. Occasionally a facial weakness lasting a few hours results from infiltration of procaine in the region of the tip of the mastoid and twice in our experience the facial weakness lasted several weeks, probably due to direct trauma to the facial nerve by the needle.

### CONCLUSIONS

1. In a patient with a demonstrated intracerebral vascular tumor in the left fronto-parietal region, hyperventilation increased the oxygen saturation of the internal jugular blood to almost arterial levels (95 per cent). This was never observed in 69 examinations of internal jugular blood of individuals without vascular tumors.

2. This procedure is suggested as an aid in the diagnosis of vascular intracranial tumors and in the evaluation of therapy.

### BIBLIOGRAPHY

1. ENGEL, G. L., FERRIS, E. B., RAPOPORT, S., LOGAN, M., and STEVENS, C. D.: Hyperventilation. II. The relation between changes in electroencephalographic mean frequency and arterial and jugular blood; simultaneous study of venous bloods of varying cranial origins. (In press.)
2. MYERSON, A., HALLORAN, R. D., and HIRSCH, H. L.: Technique for obtaining blood from the internal jugular vein and internal carotid artery, *Arch. Neurol. and Psychiat.*, 1927, xvii, 807.
3. FERRIS, E. B., and RYDER, H. W.: (Unpublished data).
4. BATSON, O. U.: Anatomical problems concerned in the study of cerebral blood flow, *Federation Proc.*, 1944, iii, 139.

# PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS, 429 PATIENTS TREATED WITH 1,200,000 UNITS IN 90 HOURS \*

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THE problem of time-dose relationship in the treatment of early syphilis has been foremost in the investigation of this mode of therapy. It has been established that doses of less than 1.2 million units of penicillin were inadequate as measured by the relapse rate.<sup>1,2</sup>

The use of a total dose of 1.2 million units of penicillin administered over different time periods, and the combination of this amount with artificial fever therapy (hypertherm) was delegated to this Center by the National Research Council.

The present report concerns only the group of patients treated by the following schedule: each patient received 40,000 Oxford units of sodium penicillin intramuscularly every three hours for 30 doses, over a period of three and three-quarter days (1.2 million units total). The results of treatment by the other schedules will form the basis of subsequent reports.

TABLE I  
Distribution by Sex and Race

Race	Total	Sex	
		Male	Female
Total	429	249*	180
Negro	362	202	160
White	66	46	20

\* Total figure includes one American Indian.

A total of 429 patients were treated by this schedule between July 19 and November 30, 1944. All patients exhibited darkfield positive lesions of primary or secondary syphilis prior to treatment. No further treatment was given unless either clinical or serologic relapse or pregnancy occurred.

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From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health in coöperation with the United States Public Health Service.

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The patients' ages ranged from four to 56 years; 74 per cent were 25 or under; 87.9 per cent were 30 or under. The distribution of patients according to sex and race is presented in table 1. The distribution according to stage of syphilis at the time of treatment is listed in table 2.

TABLE II  
Distribution of Stage of Syphilis

	Number	Per Cent
Total Diagnoses	429	100.0
Primary Syphilis	151	32.5
Seronegative	47	11.0
Seropositive	104	24.2
Early Secondary Syphilis	216	50.3
Relapse from Prev. RX	62	14.5
Relapsing Secondary	53	12.4
Monorecitive	5	1.1
Serologic	2	0.5
Neurorecurrence	1	0.25
Arseno-bismuth Resistant	1	0.25

Sixty-two of the 429 patients had received previous treatment for syphilis. This group included patients who had exhibited clinical and/or laboratory evidence of relapse after varying amounts of arsenic and bismuth, penicillin and arsenic, or penicillin alone. The remaining 367 patients had never been previously treated for syphilis.

For comparative purposes, the status of all patients and a separation of the results according to diagnosis at three-, six-, nine-, twelve- and fifteen-month intervals, after the completion of therapy, are recorded in table 3.

In 90 of the 222 patients included in "status unknown" in table 3, observation was terminated for the following reasons: 16 inducted into the armed forces; eight committed to jail; two died (cause unknown); 10 re-treated because of pregnancy, and 54 transferred to other clinics, having moved out of our jurisdiction. One hundred and two of the 222 patients were seronegative at the time of the last examination, before being lost to observation.

#### COMMENT

There were no patients whose syphilitic lesions failed to heal with this schedule of therapy. Previous experience<sup>2,3</sup> had shown that surface spirochetes disappeared with lesser amounts of penicillin than were being employed in this series; consequently, darkfield examinations were not done routinely after treatment was instituted.

Three hundred and eighty-two of the patients had been seropositive before treatment. Two hundred and thirty (60.5 per cent) achieved seronegativity after treatment. The number and per cent of patients in each stage of syphilis and the average number of days required to reach sero-

TABLE III

Number and Per Cent of Patients with Early Syphilis Treated with Penicillin from July 1, 1944 Through October 1, 1945, by Diagnosis and Treatment Results at Three Month Intervals

Diagnosis and Observation Period (Months)	Total		Failures					Clinically Negative					
			Total		Sero-logic	Clinical	Prob-able Rein-fect-ion	Sero-positive		Sero-negative		Status Unknown	
	No.	%	No.	%				No.	%	No.	%	No.	%
<b>Total:</b>													
3	429	100.0	11	2.5	1	10	—	141	32.9	150	35.0	127	29.6
6	429	100.0	42	9.8	8	33	1	62	14.4	194	45.2	131	30.6
9	429	100.0	54	12.6	11	42	1	38	8.8	182	42.4	155	36.2
12	429	100.0	72	16.8	18	53	1	21	4.9	176	41.0	160	37.3
15	429	100.0	85	19.8	24	56	5	8	1.9	114	26.5	222	51.8
<b>Primary Seronegative:</b>													
3	47	100.0	3	6.4	1	2	—	—	—	31	66.0	13	27.6
6	47	100.0	6	12.8	1	5	—	—	—	27	57.4	14	29.8
9	47	100.0	6	12.8	1	5	—	—	—	22	48.8	19	40.4
12	47	100.0	7	14.8	1	6	—	—	—	20	42.6	20	42.6
15	47	100.0	9	19.2	1	6	2	—	—	9	19.2	29	61.6
<b>Primary Seropositive:</b>													
3	104	100.0	5	4.8	—	5	—	11	10.6	51	49.0	37	35.6
6	104	100.0	11	10.6	1	10	—	5	4.8	59	56.7	29	27.9
9	104	100.0	12	11.6	1	11	—	2	1.9	53	51.0	37	35.5
12	104	100.0	15	14.5	2	13	—	1	1.0	51	49.0	37	35.5
15	104	100.0	18	17.3	4 <sup>a</sup>	14	—	—	—	33	31.7	53	51.0
<b>Early Secondary:</b>													
3	216	100.0	3	1.4	—	3	—	98	45.4	63	29.1	52	24.1
6	216	100.0	18	8.4	4	13	1	36	16.6	98	45.4	64	29.6
9	216	100.0	25	11.6	6	18	1	25	11.6	94	43.5	72	33.3
12	216	100.0	35	16.2	9	25	1	13	6.5	91	42.1	77	35.6
15	216	100.0	41	19.0	11	27	3	5	2.3	64	29.6	106	49.1
<b>Previously Treated:</b>													
3	62	100.0	—	—	—	—	—	32	51.6	5	8.1	25	40.3
6	62	100.0	7	11.3	2 <sup>a</sup>	5	—	21	33.9	10	16.1	24	38.7
9	62	100.0	11	17.7	3	8	—	11	17.7	13	21.0	27	43.6
12	62	100.0	15	24.2	6	9	—	7	11.3	14	22.6	26	41.9
15	62	100.0	17	27.4	8	9	—	3	4.8	8	12.9	34	54.9

<sup>a</sup> Includes one neurorecurrence.

negativity are presented in table 4. It is recognized that the periods of time reported are crude estimates, inasmuch as it was impossible to determine the exact day that any patient became seronegative.

All but 10 patients received a lumbar puncture before treatment was instituted. Five patients revealed abnormal cerebrospinal fluids, two of whom were neurorecurrences following previous treatment with 600,000 units of

TABLE IV

Number and Per Cent of Seropositive Cases Reaching Seronegativity, by Diagnosis, and the Average Number of Days Before Seronegativity Was Attained

Diagnosis	Seropositive	Seropositive Reaching Seronegativity		Average Number of Days Before Seronegativity Was Attained
		Number	Per Cent	
Total Patients	382	230	60.2	136.7
Primary Syphilis	104	76	73.1	91.7
Early Secondary	216	136	63.0	152.1
Relapsing Secondary	53	14	26.4	199.0
Monorecive	5	3	60.0	183.0
Serologic Relapse	2	1	50.0	358.0
Neurorecurrence	1	—	—	—
Arseno-bismuth Resist.	1	—	—	—

penicillin in three and three-quarters days. Their spinal fluid findings follow:

Patient	Date	Kahn Units	Lymphocytes	Globulin	Total Protein Mg. %	Colloidal Gold
T. S.	11/ 4/44	4	250	3+	55	1232000000
	5/23/45	4	60	1+	33	2332100000
	Deceased					
V. H.	9/26/44	0	42	2+	40	—
P. E.	10/26/44	20	50	3+	62	5554210000
L. S.	8/25/44	20	2	1+	58	1233210000
	Lost to follow-up					
B. G.	11/20/44	4	4	1+	40	2222210000
	12/ 2/44	0	2	1+	36	—
	3/10/45	0	2	1+	35	—

Eighty-five patients (19.8 per cent of the total patients treated) were known to be treatment failures at the end of 15 months' observation. These consisted of 38 relapsing secondaries; 14 primary syphilis progressing to secondary syphilis; 13 serologic relapses; eight seroresistant\* after one year's observation; five relapsing primaries (monorecive), and two neurorecurrences. Five patients were considered possible reinfections. Case histories of these patients follow:

M. L., male negro, age 20, diagnosed papular and annular secondary syphilis with eroded penile papules, Kahn titer 80 units on August 25, 1944. Received 1.2 million units of penicillin from August 26 to 29, 1944. The lesions healed promptly and 75 days after treatment the patient was seronegative. At this time he was re-admitted with the diagnosis of sulfonamide resistant gonorrheal urethritis, for which he received 150,000 units of penicillin. He remained seronegative through February,

\* Any patient with a Kahn titer of 4 units or more at the end of 12 months' observation was declared seroresistant.

1945 (186 days after treatment), at which time he presented himself with a solitary infiltrated darkfield positive penile lesion. Multiple exposures were admitted and three bouts of gonorrhea gave eloquent testimony of these exposures.

R. T., female negro, age 21, diagnosed seronegative primary syphilis on September 13, 1944. Received 1.2 million units of penicillin from September 14 to 17, 1944. The lesion healed and she remained seronegative for 257 days. She was then lost to observation until December, 1945 (470 days after treatment), at which time she presented herself with darkfield positive condylomata lata of the vulva and a Kahn titer of 80 units. The patient's husband had been admitted to this hospital a short time before with darkfield positive primary syphilis.

M. P., male negro, age 40, diagnosed secondary syphilis, eroded penile papules. Kahn titer 20 units on August 1, 1944. Received 1.2 million units of penicillin from August 2 to 5, 1944. The lesions healed and the patient was inducted into the army one month later. He stated that all serologic tests for syphilis had been negative while in the army and that he received no antisypilitic therapy. He again came under our observation in March, 1945 (233 days after treatment), at which time clinical and serologic examination revealed no abnormalities. He remained seronegative through August, 1945 (373 days after therapy), but presented himself in September (411 days after treatment) with multiple indurated darkfield positive lesions of the penis, Kahn titer 40 units. Numerous exposures were admitted.

R. C., male negro, age 18, diagnosed seronegative primary syphilis, multiple penile chancres on August 21, 1944. Received 1.2 million units of penicillin from August 22 to 25, 1944. The lesions healed and he remained seronegative through May, 1945 (283 days after treatment). On July 9, 1945 (323 days after treatment), he was readmitted with a single, indurated, darkfield positive penile lesion, Kahn titer 40 units. Multiple exposures were admitted.

A. G., female negro, age 27, diagnosed seronegative primary syphilis, chancre at fourchette, on September 18, 1944. Received 1.2 million units of penicillin from September 19 to 22, 1944. The lesion healed and she remained seronegative through September, 1945 (373 days after treatment). In January, 1946 (465 days after treatment), a Kahn titer of 40 units was found, and she was clinically negative. On her next examination (496 days after treatment) a darkfield positive chancre of the right labium majus and papular secondary syphilis were present. Gonorrheal urethritis and cervicitis were proved by bacteriologic studies. Numerous exposures were admitted.

It is interesting to note that this schedule of treatment is considerably more effective than either smaller amounts of penicillin plus arsenic, or half as much penicillin over twice the length of time.<sup>4</sup> Thus, in a study to be published<sup>2</sup> in which 339 patients were treated with 600,000 units of penicillin administered intramuscularly, 10,000 units per injection, at three hour intervals over a period of seven and one-half days, there were 97 failures, or a failure rate of 28.6 per cent. Again, in a study to be published<sup>5</sup> in a series of 107 patients receiving a combination form of treatment of 320 mg. mapharsen administered intravenously, 40 mg. daily, plus 300,000 units of penicillin intramuscularly, 5,000 units per injection, every three hours over a period of seven and one-half days, there were 34 failures or a 31.8 per cent failure rate. For the present, the administration of 1.2 million units of penicillin over a 90 hour period also promises to compare favorably with the same amount of penicillin administered over seven and one-half days.

Reactions during treatment consisted of mild pruritus, systemic and focal Herxheimer reactions, and temperature elevations, none of which necessitated termination of treatment. The temperature elevation was described as primary fever if it occurred during the first 48 hours, and secondary fever, if it occurred three days or more after the initiation of treatment. It is interesting that 25.4 per cent of the patients developed a Grade I secondary fever while being treated with penicillin alone (table 5).

TABLE V  
Number and Per Cent of Patients with Reactions

Reactions	Number	Per cent
Total patients treated	429	100.0
Primary fever	241	56.2
Grade I	132	30.8
Grade II	75	17.5
Grade III	34	7.9
Secondary fever	118	27.5
Grade I	109	25.4
Grade II	9	2.1
No reactions	70	16.3

Definitions:

Grade I: under 1 degree above pre-treatment level.

Grade II: 1 to 2 degrees above pre-treatment level.

Grade III: 2 degrees or more above pre-treatment level.

### SUMMARY

1. Four hundred and twenty-nine patients with darkfield positive syphilis were treated over a three and three-quarter day period, each receiving 1,200,000 units of sodium penicillin, given 40,000 units intramuscularly every three hours for 30 doses.

2. Eighty-five patients were considered treatment failures. (See "Failures," table 3.)

3. In our experience, this schedule of treatment appears to be more effective than smaller amounts of penicillin either alone or in combination with arsenicals administered over twice the time period.

### BIBLIOGRAPHY

1. MOORE, J. E., MAHONEY, J. F., SCHWARTZ, W., STERNBERG, T., and WOOD, W. B.: Treatment of early syphilis with penicillin; preliminary report of 1,418 cases, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 67.
2. BAUER, T. J., BUNDESEN, H. N., CRAIG, R. M., SCHWEMLEIN, G. X., and BARTON, R. L.: The treatment of early syphilis with 600,000 units of penicillin in seven and one-half days, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1947, xxxi, 45.
3. MAHONEY, J. F., ARNOLD, R. C., and HARRIS, A.: Penicillin treatment of early syphilis, *Ven. Dis. Inform.*, 1943, xxiv, 355.
4. BINKLEY, G. W., and KILE, R. L.: Rapid treatment of early syphilis with small doses of penicillin; observations in 159 cases, *Arch. Derm. and Syph.*, 1945, li, 200.
5. BUNDESEN, H. N., CRAIG, R. M., SCHWEMLEIN, G. X., BARTON, R. L., and BAUER, T. J.: The rapid treatment of early syphilis with the combined use of penicillin and mapharsen, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1946, xxx, 475.

# THE USE OF BAL (2,3-DIMERCAPTOPROPANOL) IN THE TREATMENT OF AGRANULOCYTOSIS FOLLOWING INTENSIVE ARSENOTHERAPY FOR SYPHILIS \*

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TOXIC reactions in man due to the systemic action of arsenic have been observed occasionally during routine arsenotherapy for syphilis. The recent widespread use of highly intensive schedules of anti-syphilitic treatment has markedly increased the incidence of these reactions. One of these, agranulocytosis, once considered rare, has occurred more frequently since these newer methods of arsenotherapy for syphilis have been introduced. This reaction, characterized by a disappearance of the granulocytes from the blood stream, is due possibly to the toxic action of arsenic on the blood forming organs. As a result of the loss of the granulocytes, infections occur more readily. Severe infections of the tonsils and pharynx are the most common in this condition. Treatment of this condition prior to the introduction of BAL consisted of the administration of blood transfusions, pentnucleotide and liver extract. The mortality rate of this toxic reaction has been very high, varying between 50 and 70 per cent.<sup>1, 2</sup> In the series of cases reported in this paper that were treated with BAL, no deaths occurred. Announcement of the development and properties of this substance has been withheld until recently for reasons of security.

BAL was first described by Peters.<sup>3</sup> It is an anti-arsenical, 2,3-dimercaptopropanol, that was first used by the British for Lewisite gas burns. It is from this that the name BAL (British Anti-Lewisite) is derived. Investigators have recently found that this compound is of value not only in the treatment of local arsenical reactions, but for systemic reactions as well.<sup>4</sup>

The toxicity of arsenicals has been shown to be due to the combination of the arsenic radical with the SH groups of the activating protein of enzyme systems to form a stable compound, which thereby interferes with tissue respiration.<sup>5</sup> BAL through its selective affinity for the arsenic radical may prevent or even reverse this reaction. The resulting compound is known as thio-arsenite, which is more stable and is easily excreted by the kidneys.

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The drug is dispensed in a stable solution using peanut oil with benzyl benzoate as a solvent. The dosage recommended is 2.5 mg. per kilo. at each injection. This is repeated every four hours for the first two days, then once or twice daily thereafter for six days. Adjuncts to this treatment are necessary to combat infection present in the majority of these cases. Doan<sup>6</sup> has shown through his studies on the correlation of bone marrow and peripheral blood observations that approximately two weeks may be required for the maturation of the immature myeloblast to the mature polymorphonuclear neutrophilic leukocytes. It is in this phase of the complication that the so-called "anti-biotic reprieve" is effective, and then only if the insult is of mild and temporary nature. Penicillin is the drug of choice used to effect this reprieve. If the damage to the bone marrow is so potent that the myelopoiesis is more than transiently impeded, this temporary suppression of secondary bacterial invaders is of no avail. Penicillin was used effectively in one instance but its unavailability at the time curtailed its further use.

Twelve cases of agranulocytosis occurring during arsenotherapy for syphilis were observed and all were treated with BAL. No mortality occurred in this series. All these cases occurred in patients treated with intensive arsenotherapy with the exception of one. In the latter case the complication occurred during routine therapy using neoarsphenamine. Mapharsen was the arsenical used in the remaining 11 cases.

*Case 1.* B. L., colored female, age 20, was admitted on June 3, 1944, with a diagnosis of early latent syphilis, previously treated, and gonorrheal cervicitis. She was placed on an intensive treatment schedule, consisting of 55 milligrams of mapharsen given intravenously daily, for a period of 25 days. At the same time she was given four grams of sulfathiazole daily for five days. On admission the hemoglobin was estimated at 77 per cent. The white count was 6,500, with no differential count recorded. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the eighteenth injection, when she developed a sore throat and chilly sensations and a temperature of 102.2° F. On examination there was diffuse redness, edema of the pharynx, and several ulcerated areas on both tonsils. At this time the hemoglobin was 80 per cent, the red blood count 4,410,000, and the white blood count 3,000, with a complete absence of granulocytes, 87 per cent lymphocytes, and 13 per cent monocytes. Mapharsen was discontinued and treatment with BAL instituted. The temperature remained elevated for four days, reaching a peak of 103° F., after which it fell by lysis. Granulocytes reappeared within three days, at which time the hemoglobin was 82 per cent, the red blood count 4,400,000, and the white blood count 4,000, with 90 per cent polymorphonuclear neutrophils, 1 per cent basophiles, 4 per cent lymphocytes, and 5 per cent monocytes. On the next day the white blood count was 6,600, with 24 per cent polymorphonuclear neutrophils, 68 per cent lymphocytes, and 8 per cent monocytes. On the fifth day following reaction the white blood count was 9,600, with 56 per cent polymorphonuclear neutrophils, 38 per cent lymphocytes, and 6 per cent monocytes. The patient made an uneventful recovery.

*Case 2.* O. F., colored male, age 39, was admitted on February 22, 1944, with a diagnosis of primary syphilis, seropositive, previously treated, and was placed on an intensive treatment schedule, receiving 70 milligrams of mapharsen daily for 20 days. An admission blood count was not done. The urinalysis was essentially normal.

The patient tolerated mapharsen well with the exception of mild headache and nausea following each injection. In addition to the mapharsen, he also received four grams of sulfathiazole a day for five days for the secondary infection in the primary lesion. Following the eighteenth injection of mapharsen the patient developed a temperature of 102.4° F. and complained of a sore throat. Examination revealed a necrotic lesion of both tonsils. The white blood count was 2,600, and there was a complete absence of granulocytes. He was given a 500 c.c. blood transfusion and started on BAL. The next day the white blood count was 1,000 and there was still a complete absence of granulocytes. He was given a second transfusion in 24 hours together with other supportive measures. He continued to run a septic temperature reaching 105° F. for six days, after which the temperature returned to normal. The granulocytes reappeared in the blood stream on the seventh day. Two weeks following reaction, the white blood count was 6,320, and there were 58 per cent polymorphonuclear neutrophils, 38 per cent lymphocytes, and 4 per cent monocytes. The patient made an uneventful recovery.

*Case 3.* O. D., colored female, age 17, was admitted on August 11, 1944, with a diagnosis of early latent syphilis, not previously treated, with eight months' pregnancy. She was placed on an intensive treatment schedule, receiving 60 milligrams of mapharsen daily for 25 days. On admission the hemoglobin was 55 per cent and the white blood count was 7,200, with 65 per cent polymorphonuclear neutrophils, 53 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the twentieth dose, at which time in a routine blood count it was noted that the white blood count had fallen to 3,500, with 5 per cent polymorphonuclear neutrophils, 3 per cent eosinophiles, 59 per cent lymphocytes and 3 per cent monocytes. She had no complaints. Examination revealed only a slight injection of the pharynx and the temperature was 100.8° F. Mapharsen was discontinued. On the second day after this reaction the patient went into labor and delivered a full-term living infant. She was treated with pentnucleotide, liver extract intramuscularly and BAL. She also received two 500 c.c. blood transfusions. The temperature dropped by lysis after the fourth day. The fifteenth day following the complication, the hemoglobin was 85 per cent, and the white blood count was 7,300, with 56 per cent polymorphonuclear neutrophils, 2 per cent eosinophiles, 37 per cent lymphocytes, and 5 per cent monocytes. The patient made an uneventful recovery.

*Case 4.* E. G., colored female, age 18, was admitted on July 15, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on an intensive treatment schedule consisting of 55 milligrams of mapharsen daily for 25 days. In the admission blood count the hemoglobin was 75 per cent, the white blood count was 6,300 and there were 60 per cent polymorphonuclear neutrophils, 2 per cent eosinophiles, 36 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the eighth dose, at which time the temperature rose to 102° F. The blood count and urinalysis showed no abnormal findings. Treatment was withheld for one day and small trial doses of mapharsen were given on the following three days without any rise in temperature, and so the full schedule was again resumed. Following the twentieth dose of mapharsen, a routine blood count showed the white blood count had fallen to 3,000, with a complete absence of granulocytes, 73 per cent lymphocytes and 27 per cent monocytes. At this time the temperature was elevated to 100.2° F. The patient, however, had no complaints. Mapharsen was discontinued. The following day the temperature rose to a peak of 103.6° F. and there was still an absence of granulocytes. The patient was placed on BAL and forced fluids. The temperature remained elevated for three days



and then returned to 99° F. Granulocytes reappeared in the circulating blood at the same time, so that within four days the hemoglobin was 73 per cent and the white blood count 6,400, with 44 per cent polymorphonuclear neutrophils, 2 per cent eosinophiles, 44 per cent lymphocytes, and 10 per cent monocytes. The patient made an uneventful recovery.

*Case 5.* C. R., colored female, age 25, was admitted August 8, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on an intensive schedule, receiving 55 milligrams of mapharsen daily for 25 days. On admission the hemoglobin was 60 per cent, the white blood count 6,000, with 65 per cent polymorphonuclear neutrophils, 33 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well. A routine blood count performed following the twentieth dose of mapharsen showed the white blood count 3,800, with no polymorphonuclear neutrophils, 2 per cent eosinophiles, 58 per cent lymphocytes, and 50 per cent monocytes. The same evening there was a rise in temperature to 103° F. At the same time there was noted necrotic ulceration of the gingival tissue and a small eroded area on the right tonsil. Arsenotherapy was discontinued and the patient was placed on intramuscular liver, pentnucleotide, and BAL. The following days there was a complete absence of granulocytes. On the third day after the institution of treatment for the agranulocytosis, granulocytes reappeared. The white blood count was 4,500, with 15 per cent polymorphonuclear neutrophils, 55 per cent lymphocytes, 30 per cent monocytes. Recovery was uneventful.

*Case 6.* L. C., colored female, aged 19, was admitted February 26, 1944, with a diagnosis of secondary syphilis, previously treated, and was placed on a 20-day schedule of intensive therapy, receiving 50 milligrams of mapharsen daily.

The patient tolerated mapharsen well until the tenth dose, at which time she complained of nausea and vomiting. It was noted at that time that the temperature was elevated to 100° F. and there was some injection of the conjunctivae. Treatment was withheld for one day, after which a small trial dose of mapharsen was administered. This was apparently well tolerated and treatment was resumed. Following the fifteenth dose of mapharsen, the patient developed a severe chill and her temperature rose to 105° F. Mapharsen was discontinued. Physical examination revealed marked pharyngitis. The blood count on the morning of the same day was 85 per cent hemoglobin, the white blood count was 6,100, with 65 per cent polymorphonuclear neutrophils and 35 per cent lymphocytes. That night at 10:30 a repeat blood count revealed a white blood count of 2,000 and there were 10 per cent polymorphonuclear neutrophils, 50 per cent lymphocytes, and 40 per cent monocytes. On the following day the red blood count was 4,200,000, the white blood count 2,450, with no polymorphonuclear neutrophils, 2 per cent basophiles, 4 per cent eosinophiles, 47 per cent lymphocytes, and 47 per cent monocytes. The third day following this complication, the red blood count was 3,820,000, the white blood count 2,020, with a complete absence of granulocytes, 55 per cent lymphocytes, and 45 per cent monocytes. The patient experienced a stormy course with a septic temperature and necrotic pharyngitis. She was placed on BAL and penicillin with general supportive measures. On the eleventh day following the complication, the hemoglobin was 82 per cent, white blood count was 5,600, with 21 per cent polymorphonuclear neutrophils, 75 per cent lymphocytes, and 4 per cent monocytes. The blood count returned to normal on the fourteenth day. The patient made an uneventful recovery.

*Case 7.* J. B. G., colored female, age 19, was admitted on June 12, 1944, with a diagnosis of a febrile reaction following the fourth injection of neoarsphenamine for the treatment of secondary syphilis while under the care of a private physician. On admission the patient appeared toxic, her temperature was 104° F., and she had necrotic ulcerative lesions of the pharynx and tonsils. The hemoglobin was 55 per

cent, red blood count 3,200,000 and the white blood count 4,800, with 14 per cent polymorphonuclear neutrophils, 5 per cent eosinophils, 61 per cent lymphocytes, and 20 per cent monocytes. These findings suggested the diagnosis of agranulocytosis. A blood count on the following day was essentially the same. The patient was placed on pentnucleotide, BAL and other supportive measures. The temperature remained elevated for one week and fell by lysis. During this period the number of granulocytes increased so that one week after admission, the white blood count was 12,400, with 76 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 21 per cent lymphocytes and 2 per cent monocytes. The pharyngitis cleared up rapidly and the patient made an uneventful recovery.

*Case 8.* H. P.; colored female, age 17, was admitted on October 9, 1944, with a diagnosis of early latent syphilis, previously treated, and was placed on a 25-day intensive treatment schedule, receiving 50 milligrams of mapharsen daily. In the admission blood count there was 90 per cent hemoglobin, the white blood count was 6,300, with 60 per cent polymorphonuclear neutrophils, 38 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the ninth dose, at which time she complained of itching of the feet and back, but no eruption could be seen. The temperature was elevated to 100.6° F. At this time the hemoglobin was 88 per cent, the white blood count was 4,600, with 38 per cent polymorphonuclear neutrophils, 58 per cent lymphocytes, and 4 per cent monocytes. Mapharsen was withheld for one day, following which she received a small trial dose, from which there was no apparent reaction. Treatment was then resumed with the full dose of mapharsen without difficulty until she had received the thirteenth injection. The temperature then rose suddenly to 104.6° F. and the patient complained of general malaise and sore throat. The hemoglobin was 87 per cent, the white blood count 3,600, with 6 per cent polymorphonuclear neutrophils, 82 per cent lymphocytes, and 12 per cent monocytes. There was a moderate pharyngitis and a grayish exudate covering both tonsils. Mapharsen was immediately discontinued, and the patient was placed on BAL and forced fluids. The temperature remained elevated for three days, after which it returned to normal, and by the fourteenth day the hemoglobin was 88 per cent and the white blood count was 5,000, with 46 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 39 per cent lymphocytes, and 14 per cent monocytes. The patient made an uneventful recovery.

*Case 9.* J. D., colored male, age 19, was admitted with a diagnosis of secondary syphilis, previously treated, and acute gonorrheal urethritis. The previous treatment consisted of 0.3 gram of neoarsphenamine and 20 grams of sulfathiazole. He was placed on the penicillin-mapharsen-bismuth schedule, receiving 60 milligrams of mapharsen daily for eight consecutive days. On admission the hemoglobin was 95 per cent and the white blood count 6,000, with 52 per cent polymorphonuclear neutrophils and 48 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the sixth dose, at which time the temperature was elevated to 102.6° F. The white blood count at this time was 7,000, with 75 per cent polymorphonuclear neutrophils and 25 per cent lymphocytes. Although mapharsen was omitted, the temperature continued to rise and reached a peak of 105° F. within 48 hours and then fell by lysis, reaching normal on the sixth day after the onset of the reaction. On the tenth day following discontinuance of arsenotherapy, the patient was again given 60 milligrams of mapharsen. The next day the last and eighth dose of mapharsen was given. The temperature immediately rose to 101° F., and the white blood count was 3,800, with 5 per cent polymorphonuclear neutrophils, 11 per cent eosinophils, 74 per cent lymphocytes, and 10 per cent monocytes. The patient was placed on intramuscular liver extract and BAL. Four days later the white blood count was 4,800, with 4 per cent polymorphonuclear neutro-

philes, 9 per cent eosinophiles, 63 per cent lymphocytes, and 24 per cent monocytes. Daily blood counts showed a progressive rise in the leukocytes as well as in the percentage of granulocytes.

During this whole episode the patient was never very uncomfortable, nor did he ever develop pharyngitis. The white blood count on discharge two weeks after the onset of symptoms was 8,000, with 64 per cent polymorphonuclear neutrophiles and 36 per cent lymphocytes.

*Case 10.* G. R., colored female, age 15, was admitted on July 17, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on a 25-day intensive treatment schedule, receiving 50 milligrams of mapharsen daily. On admission, the red blood count was 3,600,000, the white blood count was 10,000, with 69 per cent polymorphonuclear neutrophiles and 31 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the seventh dose, when she complained of headache and the temperature was elevated to 100° F. The patient remained on treatment in spite of this elevation, which continued until the eleventh dose of mapharsen. At this time there appeared on the extensors of the forearms and thighs a fine papular non-pruritic eruption. The temperature was again 100° F. This was interpreted as an erythema of the ninth day. Mapharsen was withheld for two days, after which treatment was resumed. Following the fifteenth dose there was a brisk rise in temperature to 102.2° F., and she complained of a sore throat. The following day a necrotic exudate was found in the pharynx. On this day the red blood count was 3,850,000 and the white blood count 3,800, with no polymorphonuclear neutrophiles, 2 per cent eosinophiles, 78 per cent lymphocytes, and 20 per cent monocytes. Treatment consisted of BAL and general supportive measures. The patient's temperature remained septic for the next three days and returned to normal by lysis on the fifth day. On that day granulocytes reappeared in the blood and there were 7,400 white blood cells, with 54 per cent polymorphonuclear neutrophiles, 10 per cent eosinophiles, 30 per cent lymphocytes, and 6 per cent monocytes. The patient made an uneventful recovery.

*Case 11.* E. W., colored female, age 18, was admitted on September 9, 1944, with a diagnosis of secondary syphilis, not previously treated, with pregnancy, and was placed on a 25-day intensive treatment schedule, receiving 55 milligrams of mapharsen daily. On admission the hemoglobin was 78 per cent, the white blood count 8,500, with 63 per cent polymorphonuclear neutrophiles and 37 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well with the exception of a daily elevation of temperature between 99° F. and 100° F. Following the nineteenth injection of mapharsen, there was a brisk rise in temperature to 102.4° F. The patient complained of a sore throat. On examination she was found to have a necrotic membrane on both tonsils and large tender cervical lymph nodes. At this time the hemoglobin was 77 per cent, the white blood count 3,100, with 7 per cent polymorphonuclear neutrophiles, 68 per cent lymphocytes, and 25 per cent monocytes. Mapharsen was discontinued and the patient was placed on BAL. The following day the white blood count was 3,700, with 5 per cent polymorphonuclear neutrophiles, 65 per cent lymphocytes, and 30 per cent monocytes. The temperature remained elevated for five days and returned to normal by lysis. At the same time the granulocytes increased rapidly, so that by the fifth day following the complication the white blood count was 8,500, with 50 per cent polymorphonuclear neutrophiles, 40 per cent lymphocytes and 10 per cent monocytes.

*Case 12.* H. C., colored female, age 18, was admitted on April 24, 1944, with a diagnosis of secondary syphilis, not previously treated, and was placed on a 25-day intensive treatment schedule, receiving a daily dose of 55 milligrams of mapharsen.

On admission the hemoglobin was 82 per cent and the white blood count 6,400. No differential count was recorded. The urinalysis was normal. Following the nineteenth injection of mapharsen the patient complained of chilly sensations and dysphagia. The temperature was elevated to 102.4° F., the pharynx was reddened and edematous, and there was a necrotic membrane over the tonsils. The cervical lymph nodes were enlarged and tender. The hemoglobin was 75 per cent, the red blood count 4,300,000, the white blood count 4,100, with a complete absence of granulocytes, 60 per cent lymphocytes and 40 per cent monocytes. A smear taken from the pharynx showed a few fusiform bacilli, a moderate number of large spirochetes and a few pus cells. Mapharsen was discontinued, and the patient was placed on BAL, pentnucleotide, and liver extract. In addition she was given two blood transfusions. On the fifth day, the temperature fell by lysis, and the peripheral blood showed a few granulocytes for the first time. On the ninth day the patient was afebrile and the white blood count was 7,700, with 38 per cent polymorphonuclear neutrophils, 10 per cent eosinophils, 40 per cent lymphocytes, and 12 per cent monocytes. The patient made an uneventful recovery.

### DISCUSSION

The histories of these patients were not unusual. None gave a history of sensitivity to any drug, although 50 per cent of the cases had been previously treated with arsenicals. The type of onset in most of the cases was classical, with general malaise, headache, fever and sore throat. However, in two cases there was no pharyngitis, either concomitant with or after the febrile reactions. The reaction occurred in the last half or near the end of treatment in the majority of cases.

Routine blood counts were normal on admission with the exception of Case 7, who was admitted with agranulocytosis. The blood picture in all the cases developing the reaction showed a leukopenia with complete absence or marked reduction of granulocytes.

The course of illness was variable, Cases 2, 6 and 10 being highly toxic, having a stormy course; the others showing milder symptoms of toxicity. The blood counts returned to normal soon after the febrile reaction had been dissipated.

Treatment was routine in all cases. BAL was given in 1.5 c.c. (10 per cent solution) doses every six hours for 48 hours; then 2 c.c. daily for six doses. In three cases multiple blood transfusions were administered. In addition to this, the following general supportive measures were given: 5 per cent dextrose solution intravenously to maintain the water balance; sodium perborate mouth washes to decrease secondary infection; and vitamin therapy. In some of the cases pentnucleotide and liver extract were given.

Inasmuch as the majority of these patients received conventional supportive treatment, clinical evaluation of the efficacy of BAL is difficult. Indeed, this is true in view of the fact that it was not feasible to carry on a control series of patients with the same disease but receiving no BAL. In spite of these difficulties, the results obtained suggest that BAL, administered early, and in proper dosage, may contribute to and accelerate the recovery

of patients having agranulocytosis caused by the parenteral administration of arsenical drugs. This may be explained by the fact that BAL, through its selective affinity for the suppressing agent, may decrease the time that is required for the bone marrow to return to its normal function.

BAL is not an innocuous drug. If the dosage level of under 3 mg./kilo. is adhered to, toxic reaction rarely occurs. But when this dosage is exceeded,<sup>3</sup> some or all of the following reactions may occur: nausea, vomiting, headache, generalized aches and pains, burning sensations in the mouth, nose and eyes; sweating, restlessness, pain in the limbs, joints and trunk muscles. These untoward reactions to BAL seldom persisted for more than 30 minutes.

### CONCLUSIONS

Twelve cases of agranulocytosis occurring during arsenotherapy of syphilis are reported. Immediate cessation of the arsenical, and early treatment with BAL was instituted. There were no deaths. The results herein described clearly reflect the therapeutic action of BAL and indicate also the necessity for both prompt and adequate treatment in order to decrease the mortality in this complication occurring in arsenical therapy.

### BIBLIOGRAPHY

1. LOVEMAN, A. B.: Toxic agranulocytosis, purpura hemorrhagica and aplastic anemia following the use of arsphenamines, *Ann. Int. Med.*, 1932, v, 1238.
2. REZNIKOFF, P.: Agranulocytosis and leukopenia, *Jr. Am. Med. Assoc.*, 1940, cxv, 128.
3. WATERS, L. L., and STOCK, C.: BAL (British Anti-Lewisite), *Science*, 1945, cii, 601-606.
4. EAGLE, HARRY: The systemic treatment of arsenic poisoning with BAL (2,3-dimercaptopropanol), *Jr. Ven. Dis. Inf.*, 1946, xxvii, 114.
5. VOEGTLIN, C., DYER, H. A., and LEONARD, C. S.: Mechanisms of the action of arsenic upon protoplasm, *Pub. Health Rep.*, 1923, xxxviii, 1882-1912.
6. DOAN, CHARLES A.: The neutropenic state, *Jr. Am. Med. Assoc.*, 1932, ic, 194.

# THE PROGNOSIS OF THE WOLFF-PARKINSON-WHITE SYNDROME \*

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MANY authors, including Wolff, Parkinson and White,<sup>1</sup> consider the prognosis of the Wolff-Parkinson-White syndrome (characterized by White et al.<sup>1</sup> essentially as: (1) a short P-R interval, (2) prolonged and deformed QRS complexes, (3) normal P-J interval, and a tendency to paroxysmal tachycardia) benign. However, in reviewing the literature there is considerable evidence to show that such is not always the case. Although this condition is frequently found on routine electrocardiographic study of patients with no cardiac complaints or physical abnormalities, it is often found in persons who have had cardiac complaints for many years. The chief complaint is palpitation and tachycardia, the latter being paroxysmal tachycardia of auricular, nodal or ventricular origin. Occasionally, other evidences of heart disease are found, which are often coincidental.

If the paroxysmal tachycardia does not occur too often or last too long the prognosis is good, but in some patients the syndrome has resulted in death. In other instances, patients with the Wolff-Parkinson-White syndrome have met with a cardiac type of death although the exact mechanism has not been ascertained. Eight patients have been collected with the Wolff-Parkinson-White syndrome who have died a cardiac type of death and in whom it is considered that the syndrome was responsible. For this reason we believe that this condition should be regarded as strongly suggestive or definite evidence of heart disease, and at least a responsible representative member of the family should have the cardiac state adequately explained and the serious possibilities indicated.

The literature reviewed revealed six instances of death, two of which were probably the result of this syndrome and four undoubtedly due to it. To this group we add two patients, one death probably due to the syndrome and another directly due to the paroxysmal tachycardia associated with the syndrome. F. N. Wilson<sup>2</sup> in 1938 reported a patient who died during an attack of paroxysmal tachycardia with no evidence of heart disease other than the presence of the Wolff-Parkinson-White syndrome. Vakil<sup>3</sup> in 1942 reported a patient with the syndrome complicated by mitral stenosis who died of congestive failure resulting from frequent prolonged attacks of paroxysmal tachycardia. In 1943 Nielsen et al.<sup>4</sup> reported a patient with paroxysmal tachycardia associated with the Wolff-Parkinson-White syndrome resulting in death. Wood, Wolferth and Geckeler<sup>5</sup> reported in 1943 a 13 year old

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boy with this syndrome who died of congestive heart failure two hours following the onset of an attack of paroxysmal tachycardia precipitated by drinking a glassful of cold water. Richard F. Ohnell<sup>6</sup> reported two fatalities in cases presenting the syndrome, one occurring during an attack of tachycardia and the other probably as a result of paroxysmal tachycardia.

#### CASE REPORTS

A brief summary of the two additional patients who met a cardiac type of death is presented below:

*Case 1.* A white female patient, age 38, of Dr. J. M. Bamber had complained of attacks for several years of palpitation and rapid heart rate which had become more frequent of late. An electrocardiogram on April 29, 1935 showed an auricular

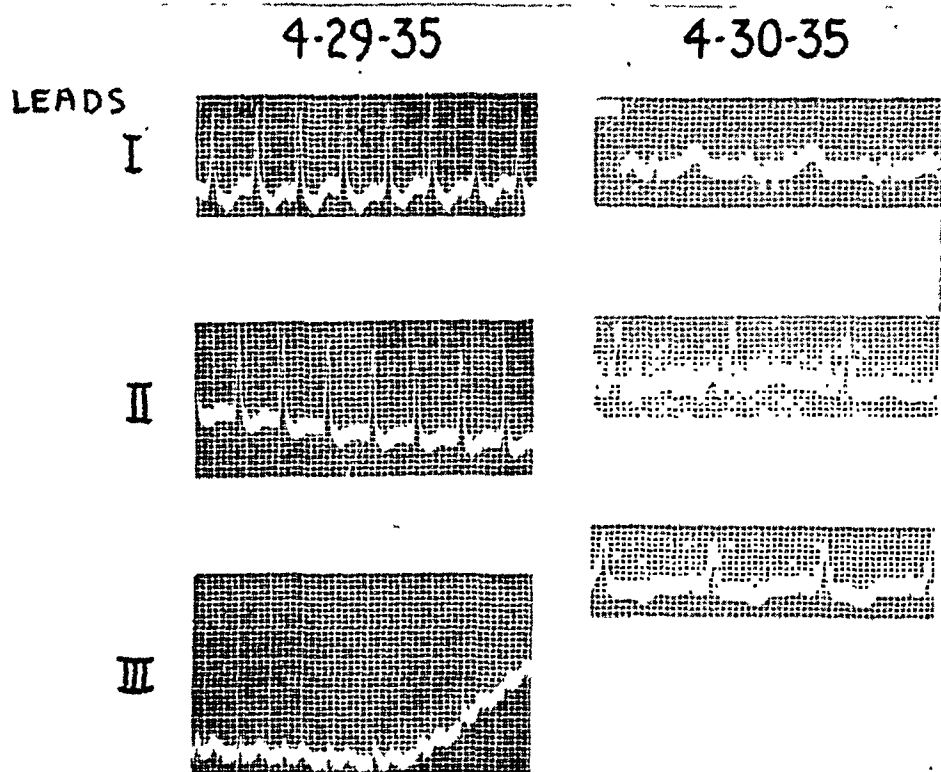


FIG. 1. The electrocardiograms of Case 1 showing a supraventricular paroxysmal tachycardia on April 29, 1935 and the Wolff-Parkinson-White syndrome on the next day when a normal sinus rhythm was established.

paroxysmal tachycardia with a rate of 240. Following quinidine therapy the rate returned to normal and the electrocardiogram showed a typical Wolff-Parkinson-White syndrome with a PR interval of 0.09 second and a QRS interval of 0.12 second (figure 1). Physical examination failed to reveal any abnormalities. Two weeks later she was found dead in bed. We assume that she died a cardiac death. Certainly it is safe to suspect a relation of the death to the Wolff-Parkinson-White syndrome.

*Case 2.* A male patient of Dr. Ralph Platou\* born normally on May 21, 1944. On June 20, 1944 he was normal on physical examination with the exception of a rapid heart which the mother had first noted at the age of two weeks. A teleroentgenogram showed a normal cardiac configuration. Paroxysms of rapid heart rate occurred at intervals of two weeks, and lasted for 12 to 24 hours, the rate usually being about 250.

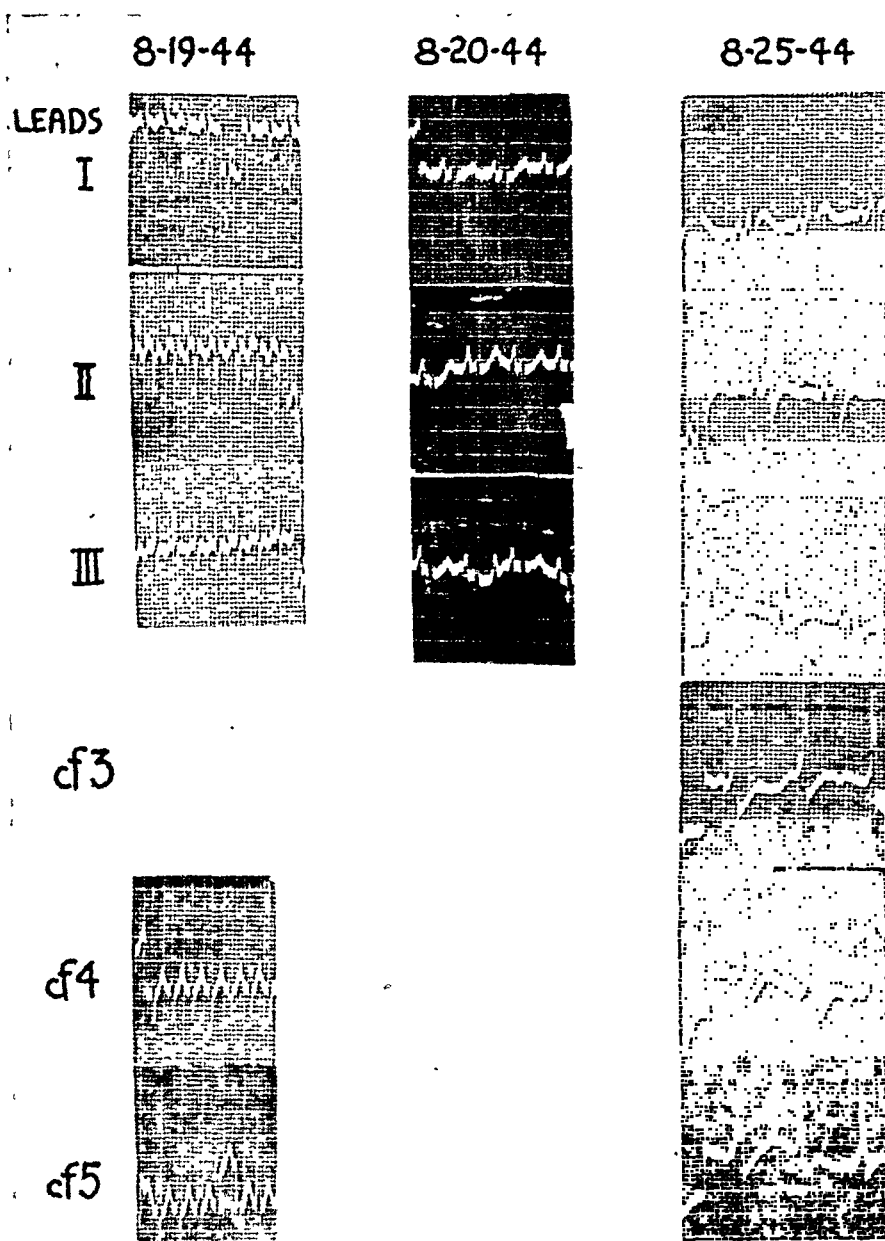


FIG. 2. The electrocardiograms of Case 2 showing a paroxysmal supraventricular tachycardia on August 19, 1944, a normal sinus rhythm with a normal conduction on August 20, 1944 and the Wolff-Parkinson-White syndrome and conduction through the aberrant bundle five days later.

\* The authors wish to express their appreciation to Drs. J. M. Bamber and Ralph Platou of Tulane Medical School for granting permissions to report these patients.



August 20, 1944 the child was hospitalized because of decompensation. He was digitalized. During his stay in the hospital electrocardiograms were recorded (figure 2). The tracing of August 19, 1944 showed paroxysmal supraventricular tachycardia. On August 20, 1944 an electrocardiogram showed a sinus tachycardia with a normal mechanism and conduction. An electrocardiogram on August 25, 1944 showed the Wolff-Parkinson-White pattern.

The attacks of paroxysmal tachycardia became more frequent and lasted longer and the congestive heart failure became more severe. A teleroentgenogram dated October 31, 1944 showed slight cardiac enlargement. On November 16, 1944 quinine sulfate was administered during an episode of tachycardia.

On January 16, 1945 another paroxysm of tachycardia resulted in a heart rate of 170-200 per minute. The next day the patient went into syncope. On January 18, generalized convulsions began at 3:00 p.m. and continued until death at 4:00 p.m.

The autopsy showed a well developed, well nourished infant with no abnormalities on gross examination of any organs, except acute dilatation of both ventricles. Examination of the heart by serial sections has been made.<sup>7</sup> Two aberrant bundles of muscle tissue have been found, one connecting the right atrium with the right ventricle and another connecting the left atrium to the left ventricle. The details of the histologic examination will be reported later.

### SUMMARY

Five deaths resulting from paroxysmal tachycardia secondary to Wolff-Parkinson-White syndrome and three additional deaths in patients with the Wolff-Parkinson-White syndrome which were probably due to paroxysms of tachycardia have been discussed. Six of the deaths were collected from the literature and two were added by this report.

With such a number of deaths associated with the Wolff-Parkinson-White syndrome it is advisable to guard the prognosis.

### BIBLIOGRAPHY

1. WOLFF, L., PARKINSON, J., and WHITE, P. D.: Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia, *Am. Heart Jr.*, 1930, v, 685.
2. WILSON, F. N.: Recent progress on electrocardiography and the interpretation of borderline electrocardiograms, *Proc. Life Insurance Med. Dir.*, 1938, xxiv, 96.
3. VAKIL, R. J.: A case of mitral stenosis with apparent bundle branch block, short PR intervals and attacks of paroxysmal tachycardia, *Indian Med. Gaz.*, 1942, lxxvii.
4. NIELSEN, A. L., MORTENSEN, V., and ESKILDSEN, P.: *Nord. med.*, 1943, xxi, 450 (quoted from reference 5).
5. WOOD, F. C., WOLFERTH, C. C., and GECKELER, G. D.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short PR interval and prolonged QRS complex, *Am. Heart Jr.*, 1943, xxv, 4.
6. OHNELL, R. F.: Preëxcitation, a cardiac abnormality, 1944, P.a. Norstedt & Soner, Stockholm.
7. DEERHAKE, H. G., KIMBALL, J. L., BURCH, G. E., and HENTHORNE, J. C.: Wolff-Parkinson-White syndrome: histological study of the cardiac septum and auriculo-ventricular groove in one case (to be published).

# BRONCHOGENIC CARCINOMA—A CLINICAL-PATHOLOGICAL STUDY OF 36 AUTOPSIED CASES SEEN AT THE BROOKLYN CANCER INSTITUTE BETWEEN 1937 AND 1945, INCLUSIVE \*

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IN recent years, because of its undoubted increase in incidence and because early recognition may lead to cure by pneumonectomy, bronchogenic carcinoma has become an increasingly important clinical entity.

This report is based on the study of a series of 36 autopsied cases of bronchogenic carcinoma seen at the Brooklyn Cancer Institute between 1937 and 1945.

## INCIDENCE

The literature of the past 10 years is replete with references to the question: Has a real increase in lung cancer been proved? The question has been reviewed exhaustively in the comprehensive monographs by Fried<sup>1</sup> and Simons.<sup>2</sup> Analysis of a total of 62,802 collected necropsies<sup>3</sup> would suggest a twenty-fold increase in lung cancer between 1900 and 1925.

Year	Relation of Primary Lung Cancers to all Cancers
1896-1901	0.54%
1902-1916	5.02%
1914-1919	6.36%
1920-1925	10.30%

It has been stated that since bronchogenic carcinoma is a disease of old age and since the average life expectancy has risen rapidly, an increase in the incidence of bronchogenic carcinoma should not be unexpected. However, Rosahn, in a careful statistical study, reached the conclusion that "the increase in pulmonary cancers observed in our autopsy material was a real and absolute increase."<sup>4</sup> This increase was definitely greater than that occurring in other malignancies.

Macklin,<sup>5</sup> applying rigidly logical criteria to the problem, has concluded that "We can merely state that *diagnosed* lung cancer is increasing at a rate which appears to be faster than that of other *diagnosed* cancers."

Peery<sup>6</sup> has emphasized two infrequently-realized facts: (1) Carcinoma of other areas can be metastatic to bronchial epithelium. (2) All the tumors formerly designated by the terms "endothelioma of the pleura," "oat-cell tumor of the mediastinum" and "tumor of the superior pulmonary sulcus" are now included in the classification of bronchogenic carcinoma, thus

\* Received for publication January 31, 1947.

swelling the statistics rather than increasing the actual incidence of the disease.

Regardless of the appearance or reality of the increase, the fact remains that bronchogenic carcinoma which was a clinical curiosity 50 years ago, has become one of the most frequently-diagnosed diseases of the lung today.

Koletsky<sup>7</sup> reviewed autopsies performed at the Cleveland City Hospital in the eleven-year period from 1927 to 1937, inclusive. There were 100 cases of primary carcinoma of the lung, constituting 1.3 per cent of 7,685 consecutive cases studied post mortem and 9.4 per cent of 1,064 cases of malignant tumor studied post mortem. At autopsy the lung ranked second only to the stomach as the primary site of carcinoma.

Jaffe,<sup>8</sup> in a similar study of 100 autopsied cases of primary carcinoma of the lung, found the lung to be the primary site in 11.4 per cent of 876 cases of malignant tumor found in a series of 6,800 consecutive autopsies. The lung ranked third, stomach first, large intestine second.

TABLE I  
Common Primary Sites of Malignancy

Primary Site	Number	Per Cent
1. Breast	75	18
2. Lung	38	9
3. Large intestine	33	7
4. Stomach	29	6
5. Cervix	28	6
6. Intraoral and pharyngeal	24	5
Tonsil	7	
Hypopharynx	6	
Palate and alveolar ridge	6	
Nasopharynx	3	
Buccal mucosa	2	
7. Non-malignant	20	5
8. Lymphosarcoma	19	4
9. Tongue	17	4
10. Bladder	14	3
11. Esophagus	13	3
12. Larynx	13	3
13. Hodgkin's disease	11	2
14. Pancreas	11	2
15. Others	99	23
Total	444	100

Of 444 autopsies performed at the Brooklyn Cancer Institute between 1937 and 1945, inclusive, bronchogenic carcinoma was found in 38 cases, an incidence of 8.6 per cent of all autopsies performed and 9.0 per cent of cases of malignancy studied post mortem. Two of these 38 cases are not included in the present report.

Many of the patients seen at this hospital are referred for radiation therapy. An analysis of the more common primary sites seen at autopsy reflects this fact in the abnormally high incidence of breast, intraoral and pharyngeal malignancies, lymphosarcoma and Hodgkin's disease (table 1).

Bronchogenic carcinoma is characteristically a disease of males who comprise 75 to 90 per cent of most reported series.<sup>1, 2, 8, 10</sup> In our series there were 32 males, an incidence of 88 per cent.

The age incidence of bronchogenic carcinoma is significantly lower than that of many common malignancies.

TABLE II  
Mean Age of Persons with Carcinoma of Various Sites <sup>4</sup>

	Number of Cases	Mean Age
Prostate	32	71.5 $\pm$ 1.9
Liver and bile ducts	26	62.7 $\pm$ 2.19
Esophagus	27	61.1 $\pm$ 1.60
Rectum and sigmoid	52	57.8 $\pm$ 1.55
Stomach	58	57.7 $\pm$ 1.41
Lung	43	55.0 $\pm$ 1.58
Uterus	29	52.2 $\pm$ 1.99

The mean age in our series was 55.1 years, almost half the cases occurring in the sixth decade.

TABLE III  
Sex and Age Incidence—Present Series

	Number	Per Cent
Sex:		
Male	32	88
Female	4	12
Age:		
30-39	1	3
40-49	8	22
50-59	16	44
60-69	11	31

Mean age: 55.1 years.

## PATHOLOGICAL, ROENTGENOLOGICAL AND CLINICAL CONSIDERATIONS

All primary bronchogenic carcinomas arise from an undifferentiated stem cell located in the basal layer of the bronchial epithelium. The tumor is an adenocarcinoma, a squamous-cell carcinoma or an undifferentiated or anaplastic carcinoma, depending on the type and degree of differentiation of the original stem cell. Tumors falling into the different histological categories have similar clinical courses, metastasize in a similar manner and show no consistent variations in their response to radiation therapy. Different series, classified by equally competent pathologists, show tremendous variations<sup>9, 10, 23, 25</sup> in the percentages of the various histological types. For these reasons such classifications may be regarded as of academic rather than of practical significance.

The earliest and most common symptom, frequently overlooked for months, is a non-productive cough. The growing tumor is a foreign body which the bronchus attempts to extrude. Soon a clear, mucoid sputum appears as the irritated bronchial epithelium attempts to wash out the foreign body. The continuous trauma of coughing together with degeneration of

the tumor produces ulceration of the surface of the growing tumor with the production of blood-streaked or purulent sputum. Because most bronchogenic carcinomas originate in the major bronchi positive diagnosis by bronchoscopic biopsy is often possible at this time. Physical examination and chest roentgenograms show no evidence of the disease in this stage.



FIG. 1. Typical roentgenographic sequence in bronchogenic carcinoma. (a) March 3, 1945, tumor mass arising from left upper hilus.

The inspiratory phase of respiration is more powerful than the expiratory phase. Consequently, as the growing tumor begins to cause partial obstruction of the bronchus, the segment of lung distal to the affected bronchus becomes emphysematous. Wheezing or asthmatic breathing may appear. The development of asthmatic breathing in middle-aged individuals should initiate a thorough search for bronchogenic carcinoma. Rarely during this stage of partial bronchial obstruction a hyperresonant percussion note, em-

physematous breath sounds and expiratory râles and rhonchi may be found on physical examination, while the roentgenogram may disclose a wedge-shaped area of decreased density with convex limiting borders.

Usually this period of emphysema is of short duration and remains unrecognized while the enlarging tumor gradually produces complete bronchial

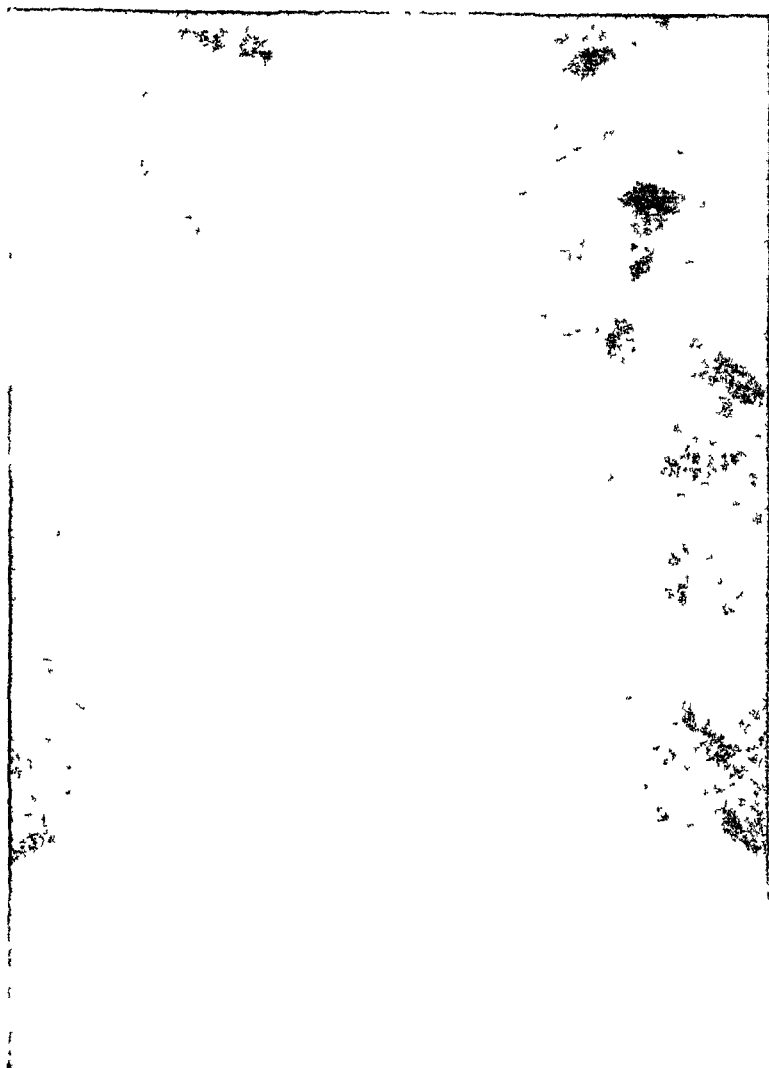


FIG. 1b. July 5, 1945, dense, wedge-shaped area of atelectasis extending beyond the tumor mass to the periphery of the lung.

obstruction and atelectasis. If the occluded bronchus is sufficiently large there may be a considerable shift of the mediastinum to the affected side. there is a real decrease in functioning lung volume and dyspnea will develop.

Almost simultaneously secondary infection develops within the atelectatic segment as necrotic tumor tissue, mucus, pus and bacteria accumulate. Leukocytosis, fever and anemia appear at this time and persist virtually un-

alterable until death. We have been impressed by the frequent early appearance of this triad, which will be discussed below.

In many cases this relentless course is interrupted by breakdown of part of the obstructing tumor. Necrotic tissue and pus are expectorated and fever and leukocytosis disappear. But tumor growth continues and leads to



FIG. 1c. November 9, 1945, phrenic nerve involvement with elevation of the left half of the diaphragm and partial atelectasis of the left lower lobe.

further bronchial obstruction with secondary infection. This cycle is responsible for the dangerous diagnosis of "recurrent pneumonia" which has been made too frequently in the face of an advancing malignancy.

The earliest and most frequent pathologic change producing physical signs is atelectasis. Over the atelectatic area diminished or absent tactile fremitus, dullness on percussion and diminished breath sounds of bronchovesicular or bronchial quality, are found. On fluoroscopy all findings, such

as mediastinal shift to the atelectatic side on inspiration, elevation of the diaphragm, paradoxical elevation of the diaphragm on inspiration and narrowing of the intercostal spaces, are the result of atelectasis. The atelectatic area itself is a dense wedge-shaped shadow with relatively indefinite concave borders extending from the hilus toward the chest wall. Fluoroscopy re-



FIG. 2. Characteristic roentgenographic appearance following complete occlusion of the left main bronchus by tumor tissue. There is a homogeneous opacity throughout the left hemithorax, the heart, mediastinum and trachea are drawn to the atelectatic side, the left half of the diaphragm is elevated and the intercostal spaces are narrowed on the left.

veals the abnormalities in respiratory dynamics; roentgenograms supply the permanent record. At this stage the tumor itself is seen in relatively few hilar cases but in most of the less common peripherally-located growths (figure 1).

Within the atelectatic areas lung tissue is destroyed by infection and tumor growth until a lung abscess which is often indistinguishable from the



usual pyogenic lung abscess develops. Not infrequently tumor cells reach the pleura where they produce a reactive hemorrhagic pleural effusion. In time sputum is aspirated into other bronchi producing numerous areas of bronchitis and pneumonitis. The physical and roentgenologic findings are those consistent with the pathological processes described (figure 2).

Roentgenological diagnosis is not always easy. Olds and Kirklin<sup>23</sup> who reviewed 206 microscopically verified cases, found that the roentgenologist was able to make a definite diagnosis of bronchogenic carcinoma or at least to suggest its presence in about 60 per cent. In the remaining 40 per cent findings were confounded with inflammatory lesions of the thorax in one-third. In another one-third a merely descriptive report was made. In the remainder various diagnoses—lymphoblastoma, metastatic carcinoma, interlobar fluid, tuberculosis, aneurysm or "negative chest"—were made.

In too many cases the tumor develops so insidiously that the presenting signs and symptoms are those of distant metastasis or local mediastinal extension. These will be considered later.

Fever, leukocytosis and anemia, characteristically accompanying many chronic infectious processes, are frequent in bronchogenic carcinoma. Yet they are barely mentioned in the literature. In 1877 Darolles<sup>13</sup> described the occurrence of fever in carcinoma of the lung. Hamman<sup>12</sup> in 1933, placed great emphasis upon the presence of fever. "Fever deserves to be mentioned on account of its importance in diagnosis. It is always present at late stages of the disease and sometimes at earlier stages as well. At early stages it is usually inconspicuous, not over 100° or thereabouts; at later stages it is often much higher. The presence of fever frequently dissuades physicians from considering the possibility of carcinoma."

In the present series a maximum temperature of 99° occurring at some time during the day was accepted as within normal limits. The temperature range during most of the hospital course was determined as closely as possible, ignoring acute febrile episodes (table 4).

TABLE IV  
Temperature Level during Hospitalization

	Number of Cases	Per Cent
Normal	8	22
99–100° F.	11	30
99–101	9	25
99–102	5	14
98–103	3	9
Total	36	100

The most frequently seen fever curve was completely irregular, reaching 100 or 101° at some time on most days. In eight cases the fever curve was more typically septic, rising to 102 or 103° late in the day after being normal or subnormal in the morning.

Paralleling fever roughly, the white cell count was frequently elevated with a moderate to marked shift to the left (table 5).

TABLE V  
Variations in White Cell Count

Total White Count	Highest	Lowest	Only Count	Not Done
Less than 10,000	1	8	5	
10-20,000	10	7	10	
20-30,000	2	1	2	
More than 30,000	3			
Total	16	16	17	3

In 16 cases multiple counts were performed. While in no case was a count higher than 30,000 white cells per cu. mm. maintained indefinitely, one leukemoid reaction was observed, in which the white cell count rose to 85,800 and dropped gradually to 30,000 during a three-month interval. Examination of the sternal marrow showed only marked leukocytosis and was suggestive of an irritative bone marrow process. Bone metastases visible by roentgenogram appeared five months after the height of the leukemoid reaction. Lisa, Solomon and Gordon<sup>14</sup> and Jackson<sup>15</sup> have reported similar leukemoid reactions in bronchogenic carcinoma.

TABLE VI  
Red Cell Count

Red Cell Count	Number
Less than 3,000,000 on one occasion	5
Less than 4,000,000	24
4-5,000,000	6
More than 5,000,000	3
Not done (terminal on admission)	3

The occurrence of anemia is mentioned only casually, if at all, in most discussions of bronchogenic carcinoma. Although rarely profound it is quite common. A count of less than 4,000,000 red cells per cu. mm. was found in 24 of 33 cases who had repeated blood counts during their hospitalizations. There was a slight but definite tendency toward increasing anemia terminally (table 6).

TABLE VII  
Final Clinical Diagnosis

Diagnosis	Number of Cases
Bronchogenic carcinoma	31
Metastatic carcinoma (primary site unknown)	2
Carcinoma of rectum	1
Lymphosarcoma of mediastinum	1
Sarcoma of chest wall	1
Total	36

## DIAGNOSIS

The diagnosis of bronchogenic carcinoma is frequently a difficult diagnosis to prove. It is of interest to examine the final diagnoses in this series of 36 cases, most of which had had several admissions to the hospital and thorough study. On five occasions the correct diagnosis was missed (table 7).

While it is rather a disturbing experience in this era of refined diagnostic technics to find a percentage of missed diagnoses as great as 14 per cent there is consolation to be found in a brief analysis of the diagnostic errors.

1. J. K. was a white male 56 years of age whose presenting symptom was swelling in the right groin shown to be an osteolytic metastasis to the right ilium. The biopsy report was anaplastic carcinoma. Although chest roentgenograms showed a mass bulging into the left lung field from the left supracardiac shadow—"probably primary bronchogenic carcinoma of the left main bronchus" according to the roentgenologist—no tumor tissue was seen on bronchoscopy. Final clinical diagnosis: Metastatic anaplastic carcinoma, primary site unknown.

At autopsy the left main bronchus was the seat of a large primary adenocarcinoma.

2. V. T. was a white male 38 years of age whose presenting symptoms were chills, night sweats, fever, substernal pain. The original chest roentgenogram taken at a district health center was reported as suggestive of pulmonary neoplasm. Bronchoscopy revealed no tumor tissue. A soft-tissue mass removed from the right thigh was diagnosed as a sarcoma microscopically. Subsequent involvement of the anterior chest wall occurred.

Final clinical diagnosis: Sarcoma of chest wall?

Carcinoma of lung?

At autopsy an anaplastic carcinoma originating in the left upper lobe bronchus was found. There were widespread metastases.

3. B. B. was a white male 61 years of age whose presenting sign was a rectal mass erroneously reported as adenocarcinoma of the rectum at another hospital. Bronchoscopy was never performed. Chest roentgenograms showed an enlarged right hilus node and terminally, consolidation of the entire right lung. Repeat biopsy of the rectal mass and biopsy of a facial nodule were both reported as anaplastic carcinoma.

Final clinical diagnosis: Carcinoma of rectum.

At autopsy an anaplastic carcinoma primary in the right lower lobe bronchus was found. There were widespread metastases to various organs including the skin and the rectal wall.

4. T. S. was a white female 49 years of age whose presenting symptom was severe low back pain of sudden onset which improved after one week of bed rest. Pain severe enough to confine the patient to bed and radiating down the back of the right thigh and leg recurred four months later. Shortly thereafter a cordotomy was performed at another hospital because of the intensity of the pain. The diagnosis at that time was: Carcinoma of unknown primary site with metastases to the pelvis and lumbar vertebrae. Ten months after the onset of pain, paraplegia developed. Roentgenograms showed a pathological compression fracture of the body of the third lumbar vertebra. It is interesting to note that at no time was a roentgenogram of the chest taken.

At autopsy an adenocarcinoma, peripherally placed in the left lower lobe, was found with metastases to nothing but the third, fourth and fifth lumbar vertebrae.

5. H. S. was a white male 50 years of age whose presenting symptoms were cough and left subcostal pain. Roentgenograms showed only a widened mediastinum. Bronchoscopy was not performed. Radiation therapy was not given until six weeks prior to death. There was no significant regression of the tumor.

Final clinical diagnosis: Lymphosarcoma of the mediastinum.

At autopsy an anaplastic carcinoma originating in the right upper lobe bronchus was found.

Jaffé<sup>8</sup> reviewed 100 autopsied cases of primary carcinoma of the lung seen at the Cook County Hospital during a six year period. During the first three year period 47.5 per cent were misdiagnosed. During the second three year period after misdiagnosed cases of bronchogenic carcinoma were presented repeatedly at clinical-pathological conferences, the percentage of misdiagnosed cases dropped to 30 per cent. Other diagnoses made in Jaffé's series were:

Carcinoma of stomach, nine cases (stomach wall had been invaded in six cases).

Tuberculosis, nine cases (five had tubercle bacilli in the sputum).

Lung abscess, three cases.

Decompensated heart, one case.

Brain tumor or central nervous system lues, six cases.

Sarcoma of bone, one case (sternal metastasis).

Carcinoma of breast, one case (breast metastasis).

Carcinoma of prostate, two cases.

It is of the utmost importance to the neurosurgeon that he be aware of the frequency with which apparent primary central nervous system tumors prove to be metastases from bronchogenic carcinoma. In Fried's<sup>1</sup> group of 49 cases of bronchogenic carcinoma, 16 showed metastases to the brain. "12 of these were admitted to the service of Dr. Harvey Cushing with the diagnosis of a tumor of the brain." Ten were operated upon.

King and Ford,<sup>11</sup> in a clinical and autopsy study of 100 cases of bronchogenic carcinoma, found metastatic deposits in the central nervous system in 27. They concluded that a careful roentgenographic study of the chest is necessary in all cases of suspected intracranial or spinal cord neoplasms and in all cases of unexplained stupor.

In the present series cerebral metastases were found at autopsy in seven cases. In two of these cases the initial symptoms, headaches and convulsions in one and gradual hemiparesis in the other, pointed to a primary brain tumor. Roentgenographic study of the chest revealed the true primary site in both cases.

The diagnosis of bronchogenic carcinoma should be suspected in the presence of any one or more of the following symptoms: Cough, sputum, chest pain or discomfort, weakness, hemoptysis or blood-streaked sputum, loss of weight, dyspnea, wheezing or hoarseness. However, in analyzing the present data, an amazing variation was found in the pattern of the presenting symptoms (table 8).

TABLE VIII  
Presenting Symptoms or Syndrome

1. Due to pulmonary involvement	24	
<i>a.</i> Cough, hemoptysis, chest pain, weight loss, repeated respiratory infections		18
<i>b.</i> Chest pain alone		2
<i>c.</i> Weight loss alone		2
<i>d.</i> Hoarseness, vocal cord paralysis		1
<i>e.</i> Pneumonia		1
2. Due to bone metastasis	7	
<i>a.</i> Low back pain (lumbar vertebrae)		5
<i>b.</i> Sudden loss of power, left arm (cervical vert.)		1
<i>c.</i> Bony swelling, right groin (ilium)		1
3. Due to brain metastasis	2	
<i>a.</i> Gradual hemiparesis		1
<i>b.</i> Headaches and convulsions		1
4. Due to other metastases	2	
<i>a.</i> To rectum (rectal mass)		1
<i>b.</i> To cervical nodes (neck mass)		1
5. Coincidental constipation	1	
Total	36	

Other unusual modes of onset, such as dysphagia, thrombosis of the superior vena cava by a compressing mass and jaundice produced by extrinsic occlusion of the common bile duct, have been reported.<sup>8</sup> It is probable that slight cough or minimal dyspnea occurred more frequently as an early but disregarded symptom. Our society, secure in the universality of the "cigarette cough," grows suspicious too late.

TABLE IX  
Methods of Obtaining Tissue for Diagnosis

	+	-	0*
1. Pleural fluid	5	6	25
2. Sputum	0	7	29
3. Bronchoscopic biopsy	10	16	10
4. Direct aspiration biopsy	2	3	31
5. Lymph node biopsy	8		
Axillary	3		
Supraclavicular	2		
Inguinal	2		
Cervical	1		
6. Subcutaneous nodules	4		
7. Thoracotomy	2		
8. Aspiration biopsy of liver	1		
9. Bone biopsy, ilium	1		

\* Key: + Positive for malignant cells.  
- Negative for malignant cells.  
0 Not done.

In the last analysis the diagnosis of bronchogenic carcinoma can be established only by the microscopic examination of an adequate biopsy specimen. In early cases the specimen is obtained either at bronchoscopy or at thoracotomy. In later stages subcutaneous nodules or involved lymph nodes can be biopsied. Pleural fluid may contain cells whose appearance is suggestive of malignancy. Sputum is rarely examined and almost never shows malignant cells when studied by older technics. However, aspiration of bron-

chial secretions at bronchoscopy and staining by Papanicolaou's method is a procedure which should be performed more often.

The following table lists the results obtained in the present series by the various methods of obtaining tissue. Thirty-three biopsies positive for malignancy were obtained in 25 patients. In 11 patients no histological proof of malignancy was obtained ante mortem. Eight of these cases died prior to 1939 when bronchoscopy was not employed routinely in every suspicious case (table 9).

### METASTASIS

Bronchogenic carcinoma spreads by direct extension, by extension to regional lymph nodes along peribronchial and perivascular lymphatics and by vascular invasion. Rarely growth along the bronchial mucosa is seen.

Most vascular invasion is venous invasion. When a malignancy at any other site invades a vein, tumor emboli are carried in the systemic circulation to the capillaries of the lung, or in the portal circulation to the sinusoids of the liver, where the tumor emboli are filtered out, grow and produce metastases. When a malignancy primary in the lung invades a vein, tumor emboli are carried to the left auricle and thence to any part of the body. It is for this reason that the appearance of metastases in bizarre locations such as the chin or thumb is characteristic of bronchogenic carcinoma rather than of malignancy primary in any other site. The various types of trophocarcinoma which metastasize in a similar manner seem to have an almost specific affinity for blood vessels.

The following table, showing the frequency with which metastases occur in multiple vital organs, summarizes the experience of several authors.

TABLE X  
Metastasis in Bronchogenic Carcinoma

To	Jaffe <sup>a</sup> 100 Autopsied Cases	Ochsner and DeBakey <sup>b</sup> 3047 Collected Autopsies	Perrone and Levinson <sup>c</sup> 38 Autopsied Cases	Present Series 36 Autopsied Cases
Thoracic lymph nodes	89%	72.2%	*	47.6%
Other lung	43	23.3	20.8%	36.4
Adrenals	42	20.3	10.4	44.8
Abdominal lymph nodes	37		20.8	14.0
Liver	36	33.3	33.8	47.6
Kidneys	28	17.5	15.6	33.6
Bones	22	21.3	5.2	39.2
Brain	19	16.5	2.6	19.6
Intestines	8	4.3		8.4
Heart	7	12.7†	13.0	5.6
Pancreas	6	7.3	13.0	11.2
Spleen	5	3.5	7.8	5.6
Peritoneum	4	4.8		5.6
Skin	2	3.6	15.6	11.2
Pericardium	2		26.0	14.0
Pleura		29.8	31.6	22.4

\* Peribronchial nodes 57.2%.

† Including pericardium. 33.8%.

Metastases were reported in occasional cases in the dura mater of the spinal cord, in thyroid, skeletal muscles, stomach, tongue, ovary, testis, breast, tonsil, diaphragm, aorta, esophagus, trachea, gall-bladder, etc.

Figures for brain and bone metastases are invariably too low because in many cases consent cannot be obtained for removing the brain and because a routine systematic examination of the bones cannot be made. In the present series bone metastases were found in 19 patients (53 per cent) during antemortem roentgen examinations. The findings were corroborated in 14 (40 per cent) of these patients at necropsy. The pelvis, femora and vertebrae were the common sites of unproved roentgen findings.

TABLE XI  
Distribution of Bone Metastases

	Bone Involved: At Necropsy	On X-Ray
Vertebrae	6	9
Ribs	5	3
Pelvis	3	8
Femur	1	4
Scapula	1	1
Sella turcica	2	1
Radius	1	1
Ulna	1	2
Humerus	1	1
Sternum	1	1

The necropsy finding of bone metastases in 40 per cent is almost twice the usually reported incidence. It is probable that complete roentgen studies will disclose bone metastases in well over 50 per cent of all cases of bronchogenic carcinoma. The discovery by roentgen examination of a solitary lytic bone metastasis should suggest the bronchus as the possible primary site, especially in men over the age of 40.

#### TREATMENT AND PROGNOSIS

Bronchogenic carcinoma runs a rapid course. Both the mean and the median life expectancy in this series were only eight months from the onset of symptoms to death. No patient lived longer than 28 months after the appearance of symptoms.

TABLE XII  
Duration of Life from Onset of Initial Symptoms

Number of Months	Number of Cases
0-3	4
4-6	6
7-9	9
10-12	5
13-15	4
16-18	3
19 and over	5

It might be noted parenthetically, that it is most difficult to determine the exact time of onset of symptoms truly referable to bronchogenic car-

cinoma. Not uncommonly initial minimal symptoms are overlooked, thus hastening the statistical course of the disease. On the other hand there are cases reported living as long as 240 months from the onset of symptoms, but without the slightest proof that these symptoms were caused by cancer.

When trained thoracic surgeons are available and when there is no discoverable evidence of metastasis, the earliest possible surgical intervention is imperative. Interval roentgen study of a suspicious pulmonary mass or hilar enlargement dooms the resectable case. Adams<sup>9</sup> who probably saw a higher percentage of early cases than are seen at the average general hospital, was able to resect only 49 of 157 cases. At the time of the report only 14, a bare 9 per cent, were living and well.

If the case is not curable surgically by pneumonectomy it is not curable. Bloch and Bogardus<sup>17</sup> reached the same conclusion in 1940 that Graham<sup>16</sup> had reached in 1936, namely, that "Up to the present (1940) irradiation has not been able to cure bronchogenic carcinoma." More encouraging results have been reported by Hocker and Guttman<sup>26</sup> with the 1,000 kilovolt roentgen therapy unit. These early results await the test of time.

Has roentgen therapy any place in the treatment of bronchogenic carcinoma? Most careful studies answer that question affirmatively.<sup>18, 19, 20, 21, 26</sup> If given before the patient has reached a preterminal state an average increase in life expectancy of about six months results. Of perhaps greater importance to the patient is the relief of pain, diminution of cough and hemoptysis, improvement in appetite and gain in weight that not infrequently follow roentgen therapy. The improvement is occasionally spectacular. One patient under observation at present (V. S.) has gained more than 20 pounds in weight during and after a course of radiation therapy. There has been no coincident roentgen evidence of improvement.

In many cases roentgen therapy produces absolutely no improvement. It is not possible to predict improvement on the basis of the microscopic cellular character of the biopsy specimen. Anaplastic carcinomas are usually regarded as the most radiosensitive. Yet Steiner<sup>22</sup> felt that "Squamous-cell carcinomas and adenocarcinomas of the lung were more radiosensitive than were the undifferentiated carcinomas which, contrary to their microscopic appearance, were either highly radioresistant or highly radiorecuperative."

Before metastases have become widespread the aim of roentgen therapy should be to administer as large a tumor dose as can be given within the limits of skin and physical tolerance. The smallest tumor dose which has been shown to produce visible histologic damage is 1,490 r.\* The carcinocidal dose is probably above 5,000 r.<sup>22</sup>

The following case received a tumor dose of 3,840 r with complete disappearance of a bronchoscopically visualized and biopsied anaplastic carcinoma. Death, caused by generalized metastases, occurred nine months after the appearance of the initial symptoms.

\* Roentgen unit.



C. K., a white male 61 years of age, was admitted to another hospital on May 13, 1940 because of a "heavy cold" and persistent productive cough of two months' duration. On physical and roentgen examination a large left pleural effusion was discovered. A chest tap was productive of bloody fluid containing cells irregular in size, shape and staining quality and strongly suggestive of malignancy. On June 11, 1940 he was referred to the Brooklyn Cancer Institute for radiation therapy.

The above findings were corroborated and, in addition, bronchoscopy revealed a mass in the left main bronchus. The biopsy report was anaplastic carcinoma. On June 29, 1940 deep roentgen-ray therapy was begun to one anterior and one posterior left upper thoracic port, 10 × 15 cm., 200 Kv., 1.8 mm. cu. Hvl., 50 cm. T S D, 200 r to two ports daily to 4,000 r in air per port. The total tumor dose was 3,840 r. Therapy was completed on August 1, 1940. Four days later a chest roentgenogram confirmed the physical findings of disappearance of the pleural effusion. No definite mass could be seen in the left lung field. On September 19, 1940 the patient was readmitted because of chest pain, weakness and progressive emaciation. Roentgenograms of the chest at this time showed only slightly increased pulmonary markings in the left lung field. Bronchoscopy on October 8, 1940 revealed that the previously-noted mass in the left main bronchus had disappeared. On November 5, 1940 numerous small hard subcutaneous nodules were noted in the abdominal wall. One of these nodules was biopsied and reported to be metastatic anaplastic carcinoma identical in all respects with the bronchoscopic biopsy of June 27, 1940. The patient grew weaker and died on December 12, 1940, nine months after the appearance of the initial symptoms.

TABLE XIII  
Patients Surviving 15 Months or More

Name and Hosp. No.	Survival After Onset of Initial Symptoms (Months)	Tumor Dose (Roentgens)	Comment
A. G. (6)	15	3600	Marked clearing of atelectasis
J. D. (165)	15	7500	Great clearing of left upper lobe atelectasis
J. D. (4074)	15	1800	No effect of radiation
H. U. (4080)	16	2800	No effect
B. B. (4120)	16	none	Antemortem diagnosis—adenocarcinoma of rectum
E. T. (3743)	17	none	Patient seen terminally
E. D. (7609)	19	none	Pneumonectomy
O. Z. (6121)	20	2000	No effect
G. S. (3199)	20	2600	1st course,
		3200	2nd course, no roentgen changes but marked clinical improvement and weight gain
F. M. (1762)	23	none	Patient seen terminally
P. K. (6944)	28	1400	No effect

At necropsy numerous metastases to subcutaneous tissue, pancreas, adrenals and liver were found. The left main bronchus was studied with the utmost care. "An area roughly 3 cm. in length which involves the terminal portion of the left main bronchus and the proximal portions of both upper and lower lobe bronchi is distinctly different in appearance from the remainder of the bronchial tree. The lining appears shiny and atrophic." On microscopic examination "the mucosa is thinner than normal. Only an occasional recognizable lining epithelial cell is present. Submucous tissue is decreased in amount. There is a scant infiltrate of lymphocytes and plasma cells. One of the larger arteries shows marked subintimal thickening. No tumor cells are present."

In this small series there were 11 patients who lived 15 or more months after the onset of symptoms. In this group there was no relation whatsoever between the tumor dose administered and longevity. Three of these patients received tumor doses of 3,600 r or more. Two showed marked clearing of atelectasis; one showed no roentgen changes but gained weight and manifested considerable clinical improvement (table 13).

Many of the 25 patients who lived less than 15 months after the onset of symptoms did not live long enough to receive a significant amount of roentgen therapy. In four cases, however, tumor doses of 3,000, 3,300, 4,000, and 3,800 r were given with survivals of only six, six, eight and eight months respectively. Only the fourth of these cases showed any effect of radiation that could be measured objectively—complete disappearance of the primary tumor (Case C. K. above).

### CONCLUSIONS

The rising incidence of bronchogenic carcinoma together with the possibility of surgical cure by pneumonectomy, demands the earliest possible diagnosis.

Bronchogenic carcinoma may soon rank first among malignancies causing death in the male.

The diagnosis of bronchogenic carcinoma must be considered in any individual past 30 years of age with symptoms or signs referable to the chest, with low back pain, with suspected cord or brain tumor or with bizarrely located metastases.

Roentgenographic study of the chest should suggest the proper diagnosis relatively early in about 60 to 75 per cent of cases of bronchogenic carcinoma.

Routine early bronchoscopy in every suspicious clinical syndrome is vital to early diagnosis and will increase the percentage of biopsy proved cases.

In many cases a major portion of the clinical course is characterized by evidence of serious pulmonary suppuration—fever, leukocytosis, anemia—whose presence should not be felt to render the diagnosis of bronchogenic carcinoma less likely.

The average life expectancy at the present time is only eight months from the onset of symptoms to death.

Demonstrable bone metastases can be found by careful roentgen study in more than 50 per cent of cases.

Every case without metastases or evidence of local invasion of vital structures should have the benefit of an exploratory thoracotomy.

Roentgen therapy although merely palliative with the generally available 200 kilovolt apparatus, should be given as early as possible after the determination of non-resectability.

Tumor doses above 5,000 roentgens should be administered if maximum benefit is to be derived.

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## BIBLIOGRAPHY

1. FRIED, B. M.: Primary carcinoma of the lung, *Medicine*, 1931, x, 373-508.
2. SIMONS, E. J.: Primary carcinoma of the lung, 1937, The Year Book Publishers, Inc., Chicago.
3. GRAHAM, E. A., SINGER, J. J., and BALLON, H. C.: Surgical diseases of the chest, 1935, Lea and Febiger, Philadelphia.
4. ROSAHN, P. D.: Incidence of primary carcinoma of the lung, *Arch. Path.*, 1940, xxix, 649-664.
5. MACKLIN, M. T.: Has a real increase in lung cancer been proved? *Ann. Int. Med.*, 1942, xvii, 308-324.
6. PEERY, T. M.: Evaluation of the apparently increased incidence of primary carcinoma of the lung, *Arch. Path.*, 1940, xxix, 625-632.
7. KOLETSKY, S.: Primary carcinoma of the lung, *Arch. Int. Med.*, 1938, lxii, 636.
8. JAFFE, R. H.: The primary carcinoma of the lung, *Jr. Lab. and Clin. Med.*, 1935, xx, 1227-1237.
9. ADAMS, R.: Primary lung tumors, *Jr. Am. Med. Assoc.*, 1946, cxxx, 547-553.
10. WASCH, M. G., and EPSTEIN, B. S.: Bronchogenic carcinoma, *Am. Jr. Med. Sci.*, 1935, cxc, 360-371.
11. KING, A. B., and FORD, F. R.: A clinical and anatomical study of neurological conditions resulting from metastases in the central nervous system due to carcinoma of the lung, *Bull. Johns Hopkins Hosp.*, 1942, lxx, 124-156.
12. HAMMAN, L.: The diagnosis of carcinoma of the lungs, *Am. Rev. Tuberc.*, 1933, xxviii, 711-733.
13. ROUBIER, C.: Les cancers fébriles du poumon, *J. de méd. de Lyon*, 1939, xx, 559-564.
14. LISA, J., SOLOMON, C., and GORDON, E. J.: Leukemoid reaction in carcinomatous skeletal and splenic metastases, *Am. Jr. Cancer*, 1940, xl, 227-230.
15. JACKSON, H., JR.: The protean character of the leukemias and the leukemoid states, *New Eng. Jr. Med.*, 1939, cxx, 175-181.
16. GRAHAM, E. A.: Primary carcinoma of the lung or bronchus, *Ann. Surg.*, 1936, ciii, 1.
17. BLOCH, R. G., and BOGARDUS, G.: Bronchogenic carcinoma, *Arch. Int. Med.*, 1940, lxvi, 39-49.
18. CHANDLER, F. G., and POTTER, C. I.: Investigation into results of x-ray treatment of primary malignant intrathoracic tumours, *Lancet*, 1927, ii, 596-598.
19. TENZEL, W. V.: Radiation therapy in carcinoma of the lung, *Jr. Am. Med. Assoc.*, 1941, cxvii, 1778-1782.
20. LEDDY, E. I.: Roentgen therapy for bronchiogenic carcinoma, *Radiology*, 1943, xli, 249-255.
21. WIDMANN, B. P.: Roentgen therapy for bronchiogenic cancer, *Am. Jr. Roentgenol.*, 1944, li, 61-69.
22. STEINER, P. E.: Effects of roentgen therapy on histologic picture and on survival in cases of primary carcinoma of lung, *Arch. Int. Med.*, 1940, lxi, 140-154.
23. OLDS, J. W., and KIRKLIN, B. R.: Primary carcinoma of the lung, *Am. Jr. Roentgenol.*, 1940, xlv, 357-369.
24. OCHSNER, A., and DEBAKEY, M.: Metastasis in carcinoma of the lungs, *Jr. Thorac. Surg.*, 1942, xi, 357.
25. PERRONE, J. A., and LEVINSON, J. P.: Primary carcinoma of the lung, *Ann. Int. Med.*, 1942, xvii, 12-25.
26. HOCKER, A. F., and GUTTMAN, R. J.: Three and one-half years' experience with the 1,000 kilovolt roentgen therapy unit at Memorial Hospital, *Am. Jr. Roentgenol.*, 1944, li, 83-94.

# PSYCHOSOMATIC ASPECTS OF CARDIAC ARRHYTHMIAS: A PHYSIOLOGICAL DYNAMIC APPROACH \*

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THE expression of emotional reactions in bodily function has been recognized and appreciated by both layman and physician since antiquity. Where the relationship between the functional disturbance and emotional upset is external, it is easily recognized and becomes amenable to treatment. However, where the disturbance is deeply rooted in the psyche, the diagnosis of the physical disorder may remain obscure and the condition then becomes resistant to the ordinary forms of therapy. Certain nosologic entities, such as peptic ulcer, mucous colitis, Graves' disease and hypertension, which a few decades ago were considered essentially somatic in origin, have been shown to be manifestations (at least in part) of a disorganized personality and often are effectively treated through psychotherapy. It is considered that in such patients pent-up energies which have failed to find proper external release develop tensions which tend to localize themselves in various organ systems, alter their natural functional capacity, and thus give expression to apparent somatic disease.

The heart is one of the most sensitive targets for stimuli of psychic origin. When such stimuli impinge frequently and over a period of time, the normal heart becomes increasingly sensitive to the slightest emotional stress, ultimately reaching a point where the individual may be continually conscious of some apparent cardiac defect. On the other hand, organic heart disease often produces emotional disturbance by creating situations of constant worry, preoccupation, and fear. Cardiac arrhythmias of any genesis may lead to dizziness, syncope, headaches and anxiety states. The interplay between the cardiovascular apparatus and the emotions is an intricate, two-way affair and it is understandable that, on occasions, the primary mechanism in the vicious cycle may be hard to determine.

Neurotic behavior accompanied by somatic complaints referable to the heart or cardiac fixation without somatic symptoms has been classified as "cardiac neurosis." It has as its central theme anxiety and fear, and is, in all likelihood, a special type of anxiety neurosis. The precipitating factors for the cardiophobia in an individual with neurotic tendencies are numerous. For instance, the unexpected death of a parent has often been responsible for

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inducing anxiety and fear of a similar fate, since in the mind of the layman, heart disease is a hereditary condition. The patient in this group may not complain necessarily of any particular symptoms, but may be worried as to "how long his heart will last." Where chest disturbances are present, whether of the thoracic cage itself or of any organ within the thorax other than the heart, the symptoms are interpreted by the patient as those arising from a diseased heart. In this group of patients careful investigation has failed to reveal any organic basis for their cardiovascular disturbances. Inquiry into the character and site of chest pain, which is a common complaint, will disclose it to be located in the apical region or left side of the thorax and characterized by protracted twinges of darting pain or of a burning sensation unrelated to physical effort. Such symptoms are characteristically different in genesis, location, and distribution from pain engendered by organic cardiac disease.

Cardiac irregularities may occur during or following an emotional episode. The patient may complain of conscious heart action, or in extreme cases, of his heart "jumping out of his throat," dizziness, and even unconsciousness. In the sensitive individual premature systoles may be very disturbing. This is well illustrated by the personal experience described by Reinhardt<sup>8</sup>: "The extrasystole has always affected me as if it were a cannon ball shot point-blank at my brain. The sensation is that of a terrific explosion occurring within the narrow and limited confines of a calcified skull, which refuses to yield to the compressive force. It is like an irresistible force against an immovable object. Most of the time I am helpless before it, and simply wait patiently in terror until the ordeal has passed. I have never been able to satisfy myself as to why I never suffered the sequelae of a cerebral accident following an extrasystole, for I can think of no other sensation which can so closely simulate breaking of a blood vessel in the brain without doing so."

It is a common experience that a neurosis developing in the course of organic heart disease or during convalescence from acute heart disease adds a definite physiological load upon the already overburdened heart. Thus, it becomes apparent that the emotional aspects of heart disease, aside from the effect of emotion upon the otherwise normal heart, are important considerations which the physician must face in outlining adequate therapy.

Attempts have been made in numerous psychiatric studies to formulate a personality pattern of patients whose chief complaints are of the disabling effects of a disturbed cardiac rhythm.<sup>2</sup> While there is merit in methods attempting to develop the personality profile of these patients, it still is best to consider such efforts as first approximations which future studies will have to define more clearly. The personality pattern has been described as follows: While these patients in many instances show marked similarity to other groups of cardiac patients, there is usually a higher incidence of familial cardiovascular disease and neurotic trends in other members of the

family. They give a history of frequent illness, either of cardiac origin or following accidents, and they have been exposed since childhood to life situations of anxiety, fear, and overindulgence by the parents. They are extremely sensitive to criticism, to which they react with a sense of impotence and repressed hostility, retreat and find release in their illness. Once their hostility is aroused, however, they react with vehemence, and when the emotion is spent, try to elicit sympathy on the basis of their cardiac condition.

The influence of emotion on the cardiac rhythm and the effects of this disturbance on the emotional life of an individual are exemplified by the following case report:

A 50-year-old white female was first seen in 1939, in the Out-Patient Department, complaining of bouts of palpitation occurring with exertion or at rest, and occasionally during sleep. These episodes would last for several hours and at times were accompanied by a sense of sternal oppression, dyspnea, fullness in the head, and by a terrifying feeling that blood was about to gush from her nostrils. She often had the impression of impending death either by hemorrhage or cardiac rupture. Between attacks there were few, if any, symptoms to indicate the presence of cardiovascular disease. There was no dyspnea on walking on flat ground and only moderate breathlessness on climbing stairs. She had no peripheral edema nor undue fatigue after a heavy day's work. Other chest discomforts, which occurred more often than the major attacks of palpitation appeared, were in the form of fleeting twinges of pain. Her other complaints were intolerance to fatty or dried foods, which, when taken, were usually accompanied by a sense of fullness and upper abdominal distress. She had these symptoms for many years prior to and after undergoing a cholecystectomy in 1935.

Physical examination revealed a well-composed, well orientated woman of average intelligence, with few positive physical findings. The cardiovascular system presented no abnormalities. The size of the heart was normal. The heart sounds were clear, regular and of good quality; the rate, 60 beats per minute; there were no murmurs; the blood pressure was 130 mm. of mercury systolic and 70 diastolic. There were no signs of peripheral vascular disease. The lungs were clear. The only abnormality in the electrocardiogram was a slight depression of S-T in Lead I, which was objectively considered as one indicating minimal, if any, damage of the heart. The roentgen-ray examination of the chest substantiated the physical findings of a normal heart and lungs. Serologic tests for syphilis were negative. Blood studies revealed a moderate hypochromic anemia; hemoglobin, 70 per cent, and the red blood cells numbered 4.4 million per cu. mm. The white count was 7.4 thousand per cu. mm., with a normal differential. The urine was negative. Sedimentation rate was 15 mm. in one hour. Fasting blood sugar was 71 mg. per cent, and the non-protein nitrogen was 35 mg. per 100 c.c. of blood. Repeated fasting blood sugars were within normal range in spite of the patient's insistence that she had been diagnosed a diabetic on various occasions.

The only significant positive finding was a high basal metabolic rate. This was repeated on numerous occasions and varied from plus 9 to plus 34 per cent. There were, however, no clinical signs, symptoms or other laboratory tests substantiating the possibility of hyperthyroidism. On the basis of her symptoms, a diagnosis of paroxysmal tachycardia (probably supraventricular) was made. The treatment consisted essentially of reassurance and sedation.

*Course:* During the ensuing six years, the patient was observed and treated by a number of physicians in the Cardiac Clinic on various occasions, without apparent relief of her symptoms. At times, she was given nitroglycerine to relieve the chest

pain, but this was without obvious effect. At other times, she was placed on therapeutic doses of digitalis, again without apparent benefit. The attacks of spontaneous palpitation became increasingly more frequent and lasted for longer periods. She was finally admitted to the Hospital in April, 1944, with a number of new and striking symptoms. She now complained of frequent vomiting, nocturia, pain in the legs, and acral paresthesia. Her dyspnea and chest pain were, in her estimation, definitely worse. Now the chest pains lasted all day and only on rare occasions were they relieved by nitroglycerine. The pain had no constant location in the chest, and, when occurring, would often radiate down to the abdomen and initiate vomiting. Regurgitation of food accompanied by a sour taste occurred after almost every meal. Again, physical examination and extensive laboratory work-up revealed no organic disease to account for her symptoms. Her basal metabolic rate on one occasion in the hospital was minus 4.7, and on another, was plus 15.7. Serial electrocardiograms showed no change from that seen six years previously. While at the hospital, all of her symptoms disappeared following mild sedation. She was discharged after remaining in the hospital for several weeks, and again was reassured as to the benign nature of her condition.

Several months later her cardiovascular symptoms reappeared. However, each time that she was examined in the clinic, the heart rate ranged from 60 to 80 beats per minute and repeated electrocardiograms failed to show any change. Finally, in February, 1946, she was re-admitted to the hospital for operation of a hallux valgus and for further investigation of her cardiac complaints. While at the hospital during preparation for this operation, she developed severe palpitation, with marked substernal oppression and symptoms of mild shock. Her pulse rate was 180, regular, and of poor quality. Her blood pressure was 180 systolic and 100 diastolic. Because of the possibility of acute myocardial infarction with a paroxysmal auricular flutter, an electrocardiogram was taken immediately and it revealed a paroxysmal auricular tachycardia. The mechanism was broken by the oral administration of 6 grains of quinidine, given every two hours. Serial electrocardiograms taken after this attack revealed a normal sinus rhythm with a rate of 80 beats per minute, without evidence of a recent infarction. She was operated upon several days later and had an uneventful recovery.

*Life Situation:* The patient, the third in a family of five, was born in Poland into an orthodox Jewish family. Her father was a good provider and managed to maintain a harmonious home life. Throughout her childhood, the patient felt closer to her father than to her mother, and respected his ideas on all her personal problems. At the age 20 years, her father arranged a marriage for her with a man many years her senior (to this day, the husband refuses to tell her his correct age). In spite of the fact that she had seen the groom only on two different occasions, she married him at the insistence of her father. Her husband, a tailor by trade, was a hard, conscientious worker, but managed to earn only enough to meet the bare necessities of living. One year after her marriage she delivered her first child. Since the family income was very meager at this time, her husband decided to leave for Chicago with better financial prospects in view. This was planned with the understanding that she meet him there at a later date. The patient took the opportunity of her husband's departure to seek a separation, but again, pressure from her father forced her to leave Poland and rejoin her husband. As in Europe, her husband's income was small, but the patient now decided to make the best of it. She became pregnant a second time, but a spontaneous miscarriage occurred. A third pregnancy followed, with the birth of a girl. Throughout her married life up to this point, her father continued giving her wise counsel by mail. She, in turn, conscious of her obligations as a mother and wife, decided to make the best of the family resources. In her own words, "I never loved my husband, although he loved me very much. Because he was a hard worker,

didn't spend money on drinking or smoking, and tried to make a living, poor as it was, for his family, I would not desert him." She shed all her love on her children and was closely associated with their personal problems. Minor illnesses up to this stage of her life were inconsequential. Then her daughter, at the age of four years, developed rheumatic fever; this was followed by repeated attacks, the child finally dying at the age of eight years. The emotional blow was so great to her that, "even today, I can't forget her." After this episode, she became more irritable and could be easily agitated by minor difficulties.

Twelve years ago, a significant event occurred in her life. While shopping, a woman standing close to her picked her pocket of \$10. Upon discovering her loss, she appealed to the manager of the store to search the woman, but he refused and reprimanded her for false accusation. That night, on returning home, she was extremely upset, depressed, worried and anxious in regard to the effect this would have on the family economy. While preparing for bed that night, she suddenly experienced severe palpitations, faintness, and she collapsed. A physician, called in to see her, diagnosed the condition as a heart attack and kept her confined to bed for two weeks. After this episode, the patient observed that any anxiety or frustration was followed by palpitation and substernal discomfort. The next "great shock" occurred five years later, when she discovered that her son, to whom she was very closely attached, had been secretly married to a girl of whom she heartily disapproved. In the patient's own words, "This girl was a well-educated person, but always sick. Every time my son brought her over, they had to leave to keep an appointment with a doctor. I think she had pelvic trouble from an abortion. I tried hard to break it up, but he married her in spite of my wishes. I have no use for my daughter-in-law; she visited me for a few minutes while I was in the hospital. I dislike her because she has taken my son's affection away from me." The complaints of palpitation, substernal discomfort, and nocturia occurred frequently, and would appear even when she was not consciously under stress. The patient felt that she could never honestly express her troubles to her friends and get worthwhile advice, so she kept them hidden within herself "to a point of bursting." She resigned herself to her lot in life and sincerely believed that she had enough insight into her difficult situations to enable her to manage them herself.

*Dream Material:* One significant dream, still vivid in the patient's memory, occurred during the pregnancy of her second child. "My father came into my dreams and told me that he was dead. He asked me to name the child after him and never to leave my husband." The next morning, she asked her husband whether he had received any letter telling of her father's death. Her husband denied such knowledge, but several weeks later, a letter from her mother informed her of her father's death. The dream had made an indelible impression upon her for the rest of her life.

*Comments:* This case clearly illustrates the problems which beset physicians trying to integrate somatic disturbances with emotional maladjustment. While physicians, regardless of background, admit the general proposition of the interplay between emotion and organ function, there is a divergence of opinion in the application to particular circumstances. The approach to the entire problem and the interpretation of the mechanisms and etiologies involved vary widely, and to a large extent depend upon the previous background of training of the physician concerned. There is need for a common meeting ground, and it can only be hoped that by the slow and painful process of evolution, this will eventually come about. Until this objective is reached, one can expect considerable overswing and apparent conflicts of opinion.



To be concrete, the physician who, after thoroughly examining the patient and finding no physical basis for his complaint, dismisses the case as one of organ neurosis, "functional," or as an "irritable organ," may overlook an important aspect. Such a diagnosis should not be made simply by the exclusion of organic findings. A very important factor in diagnosing organ neurosis is the securing of positive psychological evidence of the existence of a disturbed emotional state. This is just as important as the finding of positive roentgen-ray evidence for the diagnosis of a peptic ulcer. The psychiatrist sees the patient as one with pent-up anxieties, frustrations or suppressed hostilities which express themselves in disturbed organ function. Perhaps he has worked out personality patterns which, when noted in a patient, signify that sooner or later the patient will succumb to a particular functional disturbance.

The physiologist points to the fundamental investigations of Pavlov on conditioned reflexes and shows that the so-called organ neurosis may be interpreted as a form of conditioned reflex. Thus, it has been demonstrated that dogs, conditioned to secrete saliva in response to a given stimulus, lose this ability when the stimulus becomes one which induces fear. The physiologist, furthermore, can point to the more generalized studies of Cannon and his associates, who, starting with this fundamental concept, have elaborated the manner in which fear, anger, and the like disturb the normal economy of the human body.

Under normal physiological conditions, there is a constant dynamic fluctuation in the function of the organism as an expression of its adaptive capacity to its environment or to the immediate internal demands of one organ system upon the others. This ability to adjust and to maintain a homeostatic equilibrium is achieved in two ways: namely, (1) by the function of the autonomic nervous system, and (2) by humoral mechanisms initiated by the endocrine system. The humoral and autonomic mechanisms are not independent but interdependent in modifying specific organ activity. The older view that either the sympathetic or parasympathetic system is predominately active in personality disorders, and the consequent labelling of the patient's condition as a functional disorder of sympathetic or vagotonic origin, is too rigid a concept. Patients may show manifestations at one time suggesting sympathetic and at other times, parasympathetic dominance.

Probably a more dynamic view is that both nervous systems are called into play in the same emotional situation; the character and intensity of the emotional stimulus and the variation in the tonic state of the two parts of the autonomic nervous system determine the dominance of one system over the other for that particular circumstance. Recent studies<sup>12</sup> in our laboratory serve to illustrate the effect of autonomic influence on ectopic rhythm; thus, paroxysmal ventricular tachycardia produced by intravenously injected adrenalin was abolished by the administration of atropine, without affecting the concomitant paroxysmal hypertension. While the differentiation of

sympathetic and parasympathetic effects can be fairly sharply demonstrated in animal studies, in neurotic behavior, on the other hand, one does not ordinarily deal with so simple a pattern. One would, therefore, not expect a specific sympathetic or parasympathetic response, but, rather, one of composite character producing varying responses in the same individual on different occasions.

The summation of psychic stimuli, regardless of its pattern, must exert its effect through either one or the other subdivision of the autonomic nervous system, with modification by direct and indirect influence on the endocrine glands. These facts are applicable to disturbances in cardiac rhythm and must be accounted for in the consideration of the effect of emotional disturbances upon the beating of the heart. The direction that emotional release will take via the autonomic nervous system depends upon the path of least resistance in the organism, determined, so it would seem, by the personality profile developments since infancy. Rational analysis would, therefore, indicate that the approach to the psychosomatic problem is to blend all of these views into one general concept based on the premise of the indivisibility of psyche and soma.

The human heart, by virtue of its inherent pacemaker, is capable of rhythmic contractions when removed from the body (as has been shown in isolated hearts removed from executed criminals); nevertheless, in vivo it is under the constant influence of the central nervous system with centers located in the medulla oblongata in the floor of the fourth ventricle.<sup>11</sup> These centers are tonically active; that is, they exert their influence constantly. They consist of an inhibitory and augmentory center lying in close proximity and, due to their delicately balanced state, regulating the activity of the heart and vascular system in a smooth fashion. Their balance is adjusted to the homeostatic needs of the body. This is brought about by the impingement of impulses via afferent nerves arising from end organs of special and general sensation in somatic structures, especially from those located in the lungs, heart, and blood vessels. The most important of these visceral groups of end organs are located in the root of the aorta and in the carotid sinus. The various impulses which the cardioregulatory centers receive from these organs produce continuous reciprocal changes in the tonic balance of the two parts. Thus, while causing a depression in the tone of one, they produce a simultaneous increase in the tone of the other.

The cardioregulatory centers are influenced by impulses arising from the hypothalamus and cortex. However, there has been no clear-cut evidence that any voluntary control of the heart activity can occur. One of the rôles of these higher centers appears to be associated with automatic adjustments accompanying voluntary and involuntary activity which may result from emotional disturbances. It has been shown experimentally that cortical stimulation influences the cardioregulatory centers. Thus, faradic stimulation of the cortex adjacent to the precentral sulcus evokes pronounced

alterations in the heart rate, among other cardiovascular responses.<sup>4</sup> It is significant that these areas influencing cardiac activity are in close proximity to those of somatic function. As Fulton<sup>3</sup> has stated, "The newer disclosures concerning the cerebral cortex and the autonomic nervous system give an adequate physiological basis for the long recognized relationship between mental states and visceral processes." It is this influence of the higher centers on autonomic function and the effect of disturbed somatic functions on these centers with which psychosomatic medicine is particularly concerned.

Recent experimental work has shown that autonomic nervous regulation of the heart, as well as of blood pressure and many metabolic functions, is under the control of centers situated in the hypothalamus. Stimulation of the anterior hypothalamus produces slowing of the heart rate and prolongs A-V conduction. Stimulation of the posterior hypothalamus causes tachycardia and frequent premature systoles.<sup>1</sup> Such experimental observations are strongly suggestive of the existence of subcortical centers influencing cardiac activity. In addition, there is reason to believe that these hypothalamic centers are related to emotional expressions and that they may operate either directly upon the cardioregulatory centers or indirectly through their influence upon endocrine activities.<sup>7</sup>

Psychic impulses may, by upsetting the tonic balance in the cardioregulatory centers, cause: (1) depression or stimulation of the primary pacemaker of the heart, producing sinus tachycardia, sinus bradycardia, and sinus standstill; (2) increased irritability of subsidiary pacemakers, giving rise to paroxysmal tachycardia of supraventricular or ventricular origin or to paroxysmal auricular fibrillation and flutter, and even possibly to ventricular fibrillation with sudden death; and (3) heart block, i.e., S-A or A-V block, and more rarely, intraventricular block. The case given in detail above is an example of paroxysmal tachycardia initiated by an emotional episode. A case presented by Wedd et al.<sup>10</sup> illustrates the influence of emotional disturbances in producing S-A block in a patient with mitral stenosis.

From this brief consideration of the intricate nervous control of the heart beat, one can appreciate the wide range of influence that psychic disturbances may have in deranging the normal rhythm of the heart. The relay of activities, starting from the initiation of a psychic impulse originating in the higher brain centers to the first appearance of a disorganized heart beat, is intricate and far from being well understood. While it has been shown experimentally that the cortex, hypothalamus, the cardioregulatory centers, and endocrine systems can, when stimulated individually, cause a disturbance in cardiac mechanism, yet their coördinate activity and the relative importance of each of their rôles in carrying out this event have not, as yet, been precisely determined. It has been mentioned previously that areas have been located in the cortex which are concerned with cardiac regulation. Likewise, the hypothalamus has been demonstrated to influence cardiac

activity either through its nervous connections with the cardio regulatory centers or by its direct sympathetic connections with the cardiac plexus.<sup>1</sup> Furthermore, the hypothalamus may affect cardiac mechanism through its influence on the endocrine system, particularly on the thyroid and adrenal glands.<sup>7</sup>

The endocrine system plays a relatively important rôle in the homeostatic regulation of cardiac function.<sup>13</sup> The influence of the hormones is brought into the foreground whenever a hormonal imbalance is present in the body. Clinical and experimental observations with oral and parenteral administration of hormones have, in many instances, clarified their precise action on the cardiac mechanism. Hormones may exert their influence directly upon the heart or may act through the medium of the autonomic nervous system. A dynamic interdependence exists between these two systems. For example, unilateral stimulation of the cervical sympathetic nerves causes an increase in thyroxin output from the corresponding half of the thyroid gland; on the other hand, hormones may sensitize the autonomic nervous system, as evidenced by parenteral injection of large doses of purified thyroid or sex hormone preparations. Thus, arrhythmias which are frequently encountered in patients who are treated for obesity with large doses of thyroid extract may be accounted for on this basis.

A few examples of arrhythmias encountered in various endocrine dyscrasias will emphasize the importance of the endocrine glands in causing cardiac irregularities. Thus, rapid heart action is frequently observed in hyperthyroidism. This may occur in the form of sinus tachycardia, transient auricular fibrillation or flutter. Hypoglycemia, either as a result of pancreatic overactivity or insulin overdosage, is attended by an increase in heart rate. Tumors of the adrenal cortex and medulla are frequently associated with tachycardia. Tachycardia is common in hypofunction of the sex glands associated with the menopause. Slow heart action occurs most commonly in hypothyroidism. Hyperpituitarism associated with pituitary tumors also leads to bradycardia. Premature systoles are frequently encountered in hypoglycemic states, in hyperthyroidism, and in hyperadrenalinism. A-V or intraventricular block occurs at times in hyperthyroidism and disappears after thyroidectomy.

It would thus appear from the evidence presented that cardiac arrhythmias can result from imbalance either of the autonomic nervous system or from imbalance of the endocrine system, and that these two systems are inter-related in rather complex ways. It is further evident that emotional disturbance can operate via the nervous system to set up imbalances in the autonomic and endocrine regulation of the cardiovascular system.

In order to elucidate further the clinical aspects of psychogenic cardiac arrhythmias, it is necessary to examine briefly certain clinical aspects of the more commonly occurring arrhythmias. Cardiac irregularities often are disturbing to the patient; they lead to unpleasant sensations, and there is

a tendency to regard them as invariably signifying a disturbance of heart action, with serious implications. This is true only in instances when the irregularity complicates existing serious heart disease or when the irregularity leads to prolonged and very rapid heart action in a normal heart. In either case, the abnormal rhythm imposes a load upon the cardiovascular system sufficiently great to lead to the possibility of coronary insufficiency or congestive heart failure. It is, therefore, essential to understand the origin and mechanism involved in the various arrhythmias in order to better appreciate their clinical significance.

Arrhythmias may arise as a result of (1) disturbance in discharge of the primary pacemaker; (2) defective conduction in various parts of the heart; or (3) ectopic rhythms arising from foci in the auricles or ventricles.<sup>5</sup>

Sinus arrhythmia per se seldom causes symptoms. When present, however, in neurotic patients with heart consciousness, it may lead to palpitation, dizziness, and fainting. Prognostically, it is unimportant in normal hearts. Sinus bradycardia, while ordinarily symptomless, may cause emotional disturbances sufficient to necessitate intervention when the slowing of the heart rate becomes either profound or markedly irregular. Sinus tachycardia may appear as palpitation, dizziness, or as an unpleasant sensation over the chest, often misinterpreted as angina pectoris. In persons with coronary insufficiency, its sudden development may tend to precipitate an anginal attack. While sinus tachycardia is a mechanism by which the heart can maintain an adequate flow of blood to the tissues, when excessive, it may actually set up a vicious mechanism contributing to the development of progressive heart failure in such patients.

Depending upon the type of individual, premature systoles may or may not cause symptoms. In patients under constant tension, their presence may induce alarming symptoms, such as has been quoted earlier. The patient may be conscious of a pause after the beat or he may experience the vigorous beat that follows. In mild instances, he may be conscious of the irregularity of his heart action; in extreme instances, he may complain of sudden fullness in the chest or head, choking, or chest pain. As in the case of sinus tachycardia, the unpleasant sensation may be misinterpreted as angina pectoris and it may contribute to a cardiac fixation, especially in apprehensive individuals. Since premature systoles are inefficient beats of the heart, their frequent occurrence imposes an extra load upon the cardiac apparatus. In this respect, they may contribute to the development of congestive heart failure and to coronary insufficiency in patients already suffering from organic heart disease. On the whole, the symptoms caused by premature systoles are more alarming than their potential ill effects would justify.

Supraventricular paroxysmal tachycardia occurs at any age and is found more often in the absence than in the presence of heart disease. The history of an attack is often quite characteristic. The patient may reveal that following a disagreeable thought, a period of emotional stress, or a sudden

movement of the body, rapid heart action began abruptly. Sometimes, the attacks occur during indigestion, fatigue, infections or thyrotoxicosis. The character and severity of symptoms following paroxysmal tachycardia of supraventricular origin depend upon the duration of the attack, the emotional health of the patient, and the presence of heart disease. Patients complain of palpitation, fluttering, pounding in the chest, dizziness, faintness, smothering oppression, or substernal pain. In appearance, the patient may be pale, gray, cyanotic, dyspneic, and in extreme cases, may become comatose and develop convulsive seizures. Such cases have been misdiagnosed as epilepsy. In the presence of organic heart disease, rapid heart action contributes to a downward course leading to congestive failure, and it may be the trigger mechanism involved in precipitating angina pectoris.

Auricular flutter and auricular fibrillation occur in a paroxysmal and a chronic form. The chronic types are nearly always associated with organic heart disease; the paroxysmal types, on the other hand, occur occasionally in hypersensitive individuals following intense emotional upsets. Sino-auricular block may occur both in diseased hearts<sup>10</sup> and in normal hearts<sup>9</sup> following psychic trauma.

Consciousness of heart action such as is apt to be produced by cardiac irregularities is all too frequently misconstrued by the average individual as real heart disease. This general misconception has been inadvertently abetted in recent years by the advent of radio health talks and newspaper articles, especially those tending to dramatize cases of sudden death. While it cannot be denied that these topics are generally informative and helpful to the laity, nevertheless, they open up new avenues of thought to the super-sensitive individual, and by a process of suggestion, find fertile fields for elaboration in benign cardiac disorders. It is so easy for the uninitiated to fit signs and symptoms that they hear about into their own particular conditions and to imagine that they have serious heart disease. The cardiac death of a near relative or close friend, or even the acquaintance of a person ill with organic heart disease, often induces introspection with consequent anxiety and fear of a like fate. Similarly, a chance remark by a physician regarding the presence of a murmur, or of a premature systole, etc., to a patient whose personality makeup he has failed to assess properly, has often induced heart consciousness. Probably as notorious in this respect has been the rejection of an individual for life insurance, from the Armed Forces, or from industry because of some borderline cardiac arrhythmia which, in itself, is otherwise of no moment to the person concerned.

In psychoneurotic individuals, such situations are usually followed by anxiety and cardiac fixation, and almost invariably start him off on the usual rounds of physicians' offices. Digitalis prescribed indiscriminately by otherwise well-meaning physicians, has also shared considerably in inducing cardiac fixation. Among the laity, the administration of this drug connotes serious heart disease. The use of this agent in the treatment of

benign cardiac arrhythmias without careful explanation and assurance to the patient has, on occasion, led to irreparable cardiac invalidism.

These facts lead to the obvious deduction that the physician must take special care in obtaining a history and physical examination of such patients. A sympathetic attitude by the physician and encouragement of the patient to tell his story in his own way, while not productive of an orderly history, and while time-consuming to the busy practitioner, nevertheless, have much in their favor. They provide the means for the physician to assess the patient's personality makeup and give insight into the possible functional nature of the ailment. For the patient, these methods aid in developing confidence in the physician and set him up as a parent-ideal or substitute. Occasional interruptions and repetition of the more important statements tend to bring the idea of the benign and functional character of his complaints into the patient's conscious awareness. Ventilation of emotional conflicts often suggests to the patient their possible rôle in his present illness, and at times affords considerable psychotherapeutic benefit.

During the physical examination, the physician should be careful not to concentrate too long upon any particular region of the chest and not to appear perturbed about any physical finding that he encounters. Patients are anxious, always suspicious, and watch the physician most carefully. Training in the proper technic of performing a physical examination is as important as the scientific interpretation of the findings. Abnormal physical findings require a simple, adequate explanation of their mechanics, clarification of the significance of the emotional rôle, and assurance that the irregularity is, at most, a normal physiological variation occurring in healthy individuals. The positive physician, who is self-assured and leaves no doubt that his explanation is correct, is valuable to such a patient. The more hesitant physician, on the other hand, uncertain of the adequacy of his explanation, may actually do the patient considerable harm. These statements are especially applicable in the case of the sensitive individual, the one with easily upset emotional balance.

The confidence established in the physician by the patient, and his demonstrable interest in the patient's case, together with a complete cardiac examination and a simple explanation of the disturbance, is psychotherapy in its simplest form. A goodly percentage of patients respond to such management. In all instances, the chances of good psychotherapeutic results will depend upon the patient's inherent ability to deal with his emotional problems on the one hand and the flexibility of his life situation on the other. When the life situation does not allow for modification, and when the changes to be made depend upon the patient's capacity to adapt himself to his own environment, the treatment is long and progress becomes exceedingly slow. Removal of certain irritating factors from the patient's environment, or a complete change in surroundings yields considerable impetus towards re-

covery. This is often seen during the patient's vacation away from the strained environment of his home or office.

Cases are occasionally encountered in which psychosomatic symptoms have existed for years, have become progressively worse, and have interfered with the patient's routine of living. Such individuals have, with time, built up defenses too difficult to remove by ordinary procedures. They require careful psychoanalytic study and should be referred to the specialist.

Even though the arrhythmia has been diagnosed as psychosomatic, all aids of examination should be utilized in order to rule out every possibility of an organic basis for the irregularity. This is important, since often elimination of a somatic non-cardiac or cardiac cause of such an irregularity is the best form of therapy.

Cardiac arrhythmias of psychogenic origin, like those arising from organic causes, should be treated medically; for instance, during an acute episode of paroxysmal auricular tachycardia or flutter, the alarming symptoms of dizziness, unconsciousness or syncope must be handled as an emergency with the aid of drugs; one cannot expect psychotherapy to break such a paroxysm. Even though psychotherapy is being employed prophylactically in the treatment of some annoying arrhythmia, the therapist will find it most helpful in handling the patient if he could, at the same time, resort to simple drugs to reduce the incidence of its occurrence. The patient should be assured that the troublesome symptoms are caused by the cardiac irregularity, which experience has shown to occur in people without heart disease, and that the medicines are aimed toward the abolishment of arrhythmia per se and not toward the treatment of some basic organic disease. The drugs employed in the treatment of arrhythmias of psychogenic origin are similar to those used for cardiac irregularities arising from an organic basis.

### CONCLUDING REMARKS

It has been the purpose of this communication to delve into a subject which, in many respects, is still on the frontiers of medicine. Much of the subject matter is still unknown or inadequately surveyed; little is clearly defined. An attempt has been made to blend together various developments from the fields of psychiatry, physiology, and classical cardiology, with the view of breaking down the provincial barriers of each field in its individualistic approach to the psychosomatic problem of cardiac arrhythmias. We are aware of the imperfections which the present effort contains, but are hopeful that it will be stimulating enough to encourage the explorer in the several disciplines to widen the scope and outline the topography of this unknown wilderness. There is danger that each will see and emphasize those peculiarities for which his background has trained him to search. However, it is not too much to expect that, ultimately and perhaps sooner than we imagine, each exploration will fit as a logical, integral part into this multifaceted problem, understandable and satisfactory to all.



## BIBLIOGRAPHY

1. BEATTIE, J., BROW, G. R., and LONG, C. N. H.: Physiological and anatomical evidence for the existence of nerve tracts connecting the hypothalamus with the spinal sympathetic centers, *Proc. Roy. Soc.*, 1930, cvi, B, 253.
2. DUNBAR, F.: *Psychosomatic diagnosis*, 1943, Paul Hoeber, New York.
3. FULTON, J. F.: *Physiology of the nervous system*, 1938, Oxford University Press, New York, p. 485.
4. HOFF, E. C., and GREEN, H. D.: Cardiovascular reactions induced by electrical stimulation of the cerebral cortex, *Am. Jr. Physiol.*, 1936, cxvii, 411.
5. KATZ, L. N.: *Electrocardiography*, 2nd Edition, 1946, Lea and Febiger, Philadelphia, p. 507.
6. LEVY, A. G.: The exciting cause of ventricular fibrillation in animals under chloroform anesthesia, *Heart*, 1913, iv, 319.
7. MILLER, H. R.: *Central autonomic regulations in health and disease*, 1942, Grune and Stratton, New York, p. 184-188.
8. REINHARDT, A.: Posthumous notes on the cardiovascular system in rheumatic fever and on subacute bacterial endocarditis. Quoted from WEISS, S.: The interaction between emotional states and the cardiovascular system in health and in disease, *Lib. Ann.* Vol. 3, 1932, The International Press, New York.
9. SMITH, S. C.: The heart irregularity called "sino-auricular block," *Am. Jr. Med. Sci.*, 1921, clxii, 375.
10. WEDD, A. M., and WILSON, D. C.: Standstill of the heart of vagal origin, *Am. Heart Jr.*, 1930, v, 493.
11. WIGGERS, C. J.: *Physiology in health and disease*, 1937, Lea and Febiger, Philadelphia, p. 548.
12. WILBURNE, M., ROBBARD, S., SURTSHIN, A., and KATZ, L. N.: (Unpublished report).
13. ZONDEK, H.: *The diseases of the endocrine glands*, 1944, Williams and Wilkins Co., Baltimore.

# PRIMARY ATYPICAL PNEUMONIA \*

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PRIMARY atypical pneumonia is, in many respects, one of the most peculiar of the infectious diseases of man. In the past eight years many careful and extensive studies of the illness have been carried out. During World War II the disease occurred frequently and among military personnel the incidence was greater than that of all other forms of pneumonia combined. Since the war the incidence of the illness appears to have diminished markedly. Although there is now a considerable quantity of accurate information about the condition, there remain in an unsatisfactory state a number of important problems. From the clinical standpoint these are concerned chiefly with the establishment of the diagnosis, the differentiation of the disease from other forms of pneumonia, and its treatment. From the laboratory standpoint they are concerned chiefly with the etiology of the disease, with means whereby the diagnosis may be supported, and with the control of the condition.

In this paper present evidence regarding diagnosis on the basis of both clinical and laboratory findings will be presented and an attempt will be made to evaluate present information relative to etiology.

In primary atypical pneumonia the usual clinical picture<sup>1</sup> is the following: The onset is gradual and ill-defined; general complaints and constitutional symptoms are first noticed and commonly precede symptoms referable to the respiratory tract. Fever, cough, headache and malaise develop early and are among the commonest symptoms. Cough is almost invariably present; in its absence, the diagnosis is questionable. Usually the cough is non-productive and hacking at onset but later becomes productive; the sputum is mucoid or mucopurulent, seldom contains blood, and may be copious. Most patients do not appear very ill. Fever is usually not high and often remittent. The pulse rate is slow in relation to the fever; relative bradycardia occurs in two-thirds of cases and is of some diagnostic importance. The respiratory rate is usually normal at rest. Abnormal physical signs are not striking; often the presence of pneumonia is not suspected until roentgen-rays of the chest are taken. Roentgenograms usually show definite evidence of pneumonia; the pulmonary lesions vary widely in density and distribution. It is very doubtful that a diagnosis can be made from roentgenological evidence alone. Pneumonia is most frequently present in the lower lobes, but any area in the lungs may be affected. Consolidation may be present in more than one lobe and extension from one lobe to another may

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occur. The leukocyte count and differential patterns are usually normal. The erythrocyte sedimentation rate is increased. The blood culture is sterile. Cultures of the throat or sputum show the normal bacterial flora.

The course is extremely variable. On the average, fever is present for 10 days; the range is one day to seven weeks. The average maximum temperature is 103° F.; the range, 99 to 106° F. Fever usually falls by lysis and resolution often begins when the temperature comes to normal. However, evidences of consolidation may persist for some time. Complications are uncommon and rarely of much significance. Pleuritis occurs rarely. Hemolytic crises and anemia have been reported. Thrombophlebitis or bronchiectasis occasionally develop. The prognosis is in general excellent.

It is seldom an easy matter to establish a trustworthy diagnosis. To a large extent the diagnosis is one of exclusion. Often it is necessary to accumulate considerable clinical, roentgenological and laboratory data before the probability of error becomes small. A number of viral and rickettsial diseases may present very similar clinical pictures. These diseases are: psittacosis or ornithosis, Q fever or *Rickettsia burneti* pneumonia, influenza A, influenza B, and lymphocytic choriomeningitis. Pneumococcal as well as other bacterial pneumonias may be almost indistinguishable from primary atypical pneumonia. In children pneumonia associated with measles or whooping cough may present an analogous picture. Pulmonary tuberculosis, tularemia, coccidioidomycosis or toxoplasmosis may at times simulate the disease.

There are two laboratory procedures<sup>2-5</sup> which are helpful in supporting the diagnosis. Both are relatively simple tests which any good bacteriological laboratory should be able to carry out with ease. They are: (1) cold hemagglutination, and (2) streptococcus MG agglutination. Either test is best carried out with specimens of serum obtained at different periods during the disease, preferably at weekly intervals. If either serological test is positive, and especially if a significant increase in either type of agglutination titer is demonstrable some weeks after onset, there is a high probability that the diagnosis is correct. If both tests are negative, the diagnosis may still be primary atypical pneumonia, but to establish it beyond doubt under such circumstances is very difficult indeed.

The treatment of the disease is still in an unsatisfactory and nonspecific state. Supportive and symptomatic therapy similar to that used commonly in other forms of pneumonia is helpful but chemotherapy is of no avail. None of the sulfonamide drugs, even in very large doses, exerts a favorable influence on the course of the illness. Moreover, penicillin, even in massive dosage, is not beneficial. Convalescent human serum has been tried but has not produced any obvious effect. Fortunately, the mortality rate is very low, probably less than 0.5 per cent in previously healthy persons, and patients who appear to be severely ill generally recover from the infection. Second attacks have been observed occasionally and, therefore, it appears that the

disease is not always followed by the development of immunity against reinfection.

In 1943 it was shown that a number of very peculiar and unusual serological phenomena occur during the illness. Peterson et al.<sup>2</sup> and Turner<sup>3</sup> showed that the serum of patients may acquire the capacity to cause agglutination of human group O erythrocytes at icebox temperature but not at incubator temperature, i.e., cold-hemagglutination. Thomas et al.<sup>4</sup> found that during the disease the serum of patients may acquire the property of showing positive complement fixation reactions with a variety of animal lung tissue antigens, i.e., nonspecific complement fixation. As a result, transient positive Wassermann or Kahn reactions may be obtained during the illness. Thomas et al.<sup>4</sup> further demonstrated that in the course of the infection patients may develop in their blood specific agglutinins against a particular species of non-hemolytic streptococcus, i.e., streptococcus MG. These three serological reactions are caused by distinct and different components of serum.<sup>5</sup>

TABLE I  
Serological Reactions in Primary Atypical Pneumonia  
Summary of Published Data <sup>2-6, 14-23</sup>

Serological Test	Serum from Patients with	No. Patients Tested	Positive Test	
			No.	Per Cent
Cold hemagglutination	Prim. atyp. pneum.	801	454	56.7
Cold hemagglutination	Other diseases	1719	75	4.4
Cold hemagglutination	Normal persons	209	17	8.1
Strep. MG agglutination	Prim. atyp. pneum.	669	294	44.0
Strep. MG agglutination	Other diseases	568	23	4.0
Strep. MG agglutination	Normal persons	357	19	5.3
Complement fixation vs. lung antigens	Prim. atyp. pneum.	35	25	71.4
Complement fixation vs. lung antigens	Other diseases	23	0	0.0

Numerous studies on the serological reactions which are obtained in the disease have been carried out. A summary of published results <sup>2-6, 14-23</sup> is presented in table 1. It will be seen that positive cold-hemagglutination tests occurred in 56 per cent of patients with primary atypical pneumonia; at least 12 times more commonly than in other diseases. It will also be noted that positive streptococcus MG agglutination tests were obtained in 44 per cent of patients with primary atypical pneumonia; at least 10 times more frequently than in other illnesses. It is evident that with neither agglutination test are positive results obtained in all cases. Some patients show positive reactions with one test but not with the other. Consequently it is wise to carry out both tests as a routine. A significant increase, i.e., a four-fold increment, in titer in either test is only very rarely found in diseases

other than primary atypical pneumonia. In order to show such an increase in titer, it is necessary to test two specimens of serum, one taken early in the disease preferably less than one week after onset, and another obtained during the third or fourth week from onset. In obtaining serum from patients with the illness there is one simple precaution which should be observed. The blood is allowed to coagulate at room temperature and the serum is removed before the specimen is refrigerated. Once the serum has been separated from the clot, it may be stored at icebox temperature in the usual manner. If this procedure is disregarded and blood is allowed to coagulate in the refrigerator, the greater part or all of the component responsible for the cold-hemagglutination reaction will be removed from the serum and discarded with the clot. The results of cold-hemagglutination tests with serum separated after refrigeration will, in the great majority of instances, be negative.

It might be thought that cases which show positive cold-hemagglutination reactions or positive streptococcus MG agglutination reactions are examples of an illness different from that in cases which fail to show positive reactions in either test. This probably is not true. In both tests the serum titers commonly observed are not very high; in other words, neither test can be considered to be very sensitive. Moreover, in either test the incidence of positive reactions is directly proportional to the severity or the duration of the illness; the more severe the infection, the more probable is a positive serological reaction.<sup>1, 23</sup> It appears, therefore, that quantitative factors, e.g., the degree of illness or the extent of the infection, rather than qualitative factors, e.g., possible differences in cause, are decisive in determining the appearance of positive serological reactions.

In carrying out cold-hemagglutination tests most workers now use a 1.0 per cent suspension of group O erythrocytes. Serum titers of 1:40 or more are generally considered to be significant. A fourfold or greater increase in the titer of serum obtained during the third or fourth weeks, as compared to the titer of serum taken early in the disease, is of much greater significance and only very rarely occurs in any other condition.

In agglutination tests with streptococcus MG a 5 times concentrated and heat-killed bacterial suspension is satisfactory. Serum titers of 1:20 or more are considered to be significant. A fourfold or greater increase in agglutination titer with serum specimens similar to those mentioned above is almost never encountered except in primary atypical pneumonia.

There is now good evidence that the great majority of cases of the disease are not attributable to infectious agents, either microbial or viral, of definitely established pathogenicity for man.<sup>1, 7</sup> The following infectious agents are of little or no importance in the etiology: the psittacosis group and the influenza group of viruses; Q fever rickettsiae; and bacterial species commonly associated with pneumonia. However, a number of different infectious agents have been put forward as possible etiological factors.<sup>8-13</sup> Many attempts have been made to recover the infectious agent or agents

responsible for the disease, but there is not yet complete agreement among investigators as to the nature and identity of the causal agent. Two kinds of studies have been carried out; in one, attempts were made to transmit the infection to laboratory animals; in the other, attempts were made to transmit the infection to human volunteers.

The various results obtained in laboratory animals are confusing and conflicting. A summary of published data<sup>8-13</sup> is presented in table 2. It appears that at least five different infectious agents, each of which may be a virus, have been implicated as possible etiological factors. It is, of course, possible that a variety of different infectious agents are capable of inducing

TABLE II  
Studies on the Etiology of Primary Atypical Pneumonia  
Summary of Published Data

Reference	Susceptible Experimental Animals	Filterable Agent	Evidence for Neutralizing Antibodies in Patients
Stokes et al., <sup>8</sup> 1939	Mice, guinea pigs, ferrets	+	0
Weir and Horsfall, <sup>9</sup> 1940	Mongoose, chick embryo	+	+
Blake et al., <sup>10</sup> 1942	Cats, kittens	+	+
Eaton et al., <sup>11</sup> 1942	Cotton rats	+	0
Horsfall et al., <sup>12</sup> 1943	Cotton rats	+	+
Eaton et al., <sup>13</sup> 1944	Chick embryo, hamsters, cotton rats	+	+

the disease, and that at different times and places one or another of these agents was recovered. However, it should be pointed out that none of the reports concerned with filterable infectious agents has been confirmed by an independent report from another laboratory. Unfortunately, all of the agents which have been claimed to be transmissible to laboratory animals possessed properties which made experiments difficult to carry out and the results obtained even more difficult to interpret. The results of virus neutralization tests with sera from patients were considered to indicate that neutralizing antibodies against most of the agents had developed during the illness. Convincing evidence for the development of antibodies against a virus would provide strong evidence in favor of a causal relationship. However, because of the very peculiar serological phenomena which are associated with the illness and the very low pathogenicity of the infectious agents so far employed, it is doubtful that unequivocal evidence for the development of antibodies against a virus has been obtained.

The results of experimental transmission of the disease in human volunteers carried out by the Commission on Acute Respiratory Diseases<sup>22</sup> appear to have been more decisive than results obtained in laboratory animals. Among 60 men who were inoculated with pooled specimens of throat washings and sputa obtained from patients, 16 developed an illness which was thought to be primary atypical pneumonia, whereas 26 others developed so-called minor respiratory illness without pneumonia. It was shown that

bacteria-free filtrates were capable of inducing the disease in man and that the experimental infection could be transmitted a second time in volunteers. Among the 16 volunteers in whom the disease was apparently induced, 13 developed cold hemagglutinins and two also developed agglutinins against streptococcus MG. These workers concluded that the results of their studies indicate that the disease is at least initiated, if not caused, by a filter-passing agent, presumably a virus.

Not only have various viruses been suggested as etiologic agents in the disease, but also a bacterium has been implicated in the pathogenesis. A single serological type of non-hemolytic streptococcus, now designated streptococcus MG, was isolated from the lungs of fatal cases.<sup>5</sup> As has been indicated, agglutinins against this microorganism develop in the serum of approximately 44 per cent of patients. Present evidence indicates that the various serological reactions obtained with streptococcus MG are caused by specific antibodies against it which are separate and distinct from the serum components responsible for cold-hemagglutination and nonspecific complement fixation. There appear to be three possible explanations of the serological findings with respect to streptococcus MG. First, they may be due to a coincidental immunological relationship to the actual causal agent. Second, they may be due to secondary invasion by streptococcus MG. Third, they may be the result of a so-called complex or double infection initiated by both the streptococcus and some other infectious agent, presumably a virus. There are some reasons for thinking that the first two explanations are improbable. However, it has not been possible, as yet, to obtain direct and conclusive evidence in favor of the theory of complex infection.

#### BIBLIOGRAPHY

1. CURNEN, E. C., MIRICK, G. S., ZIEGLER, J. E., JR., THOMAS, L., and HORSFALL, F. L., JR.: Studies on primary atypical pneumonia. I. Clinical features and results of laboratory investigations, *Jr. Clin. Invest.*, 1945, xxiv, 209-226.
2. PETERSON, O. L., HAM, T. H., and FINLAND, M.: Cold agglutinins (autohemagglutinins) in primary atypical pneumonias, *Science*, 1943, xcvi, 167.
3. TURNER, J. C.: Development of cold-agglutinins in atypical pneumonia, *Nature*, 1943, cli, 419-420.
4. THOMAS, L., MIRICK, G. S., CURNEN, E. C., ZIEGLER, J. E., JR., and HORSFALL, F. L., JR.: Serological reactions with an indifferent streptococcus in primary atypical pneumonia, *Science*, 1943, xcvi, 566-568.
5. THOMAS, L., MIRICK, G. S., CURNEN, E. C., ZIEGLER, J. E., JR., and HORSFALL, F. L., JR.: Studies on primary atypical pneumonia. II. Observations concerning the relationship of a non-hemolytic streptococcus to the disease, *Jr. Clin. Invest.*, 1945, xxiv, 227-240.
6. THOMAS, L., CURNEN, E. C., MIRICK, G. S., ZIEGLER, J. E., JR., and HORSFALL, F. L., JR.: Complement fixation with dissimilar antigens in primary atypical pneumonia, *Proc. Soc. Exper. Biol. and Med.*, 1943, lii, 121-125.
7. Commission on Acute Respiratory Diseases: The present status of the etiology of primary atypical pneumonia, *Bull. N. Y. Acad. Med.*, 1945, xxi, 235-262.
8. STOKES, J., JR., KENNEY, A. S., and SHAW, D. R.: New filterable agent associated with respiratory infections, *Trans. and Studies Coll. Phys. Philadelphia*, 1939, vi, 329-333.

9. WEIR, J. M., and HORSFALL, F. L., JR.: The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, *Jr. Exper. Med.*, 1940, lxxii, 595-610.
10. BLAKE, F. G., HOWARD, M. E., and TATLOCK, H.: Feline virus pneumonia and its possible relation to some cases of primary atypical pneumonia in man, *Yale Jr. Biol. and Med.*, 1942, xv, 139-166.
11. EATON, M. D., MEIKLEJOHN, G., VAN HERICK, W., and TALBOT, J. C.: An infectious agent from cases of atypical pneumonia apparently transmissible to cotton rats, *Science*, 1942, xcvi, 518-519.
12. HORSFALL, F. L., JR., CURNEN, E. C., MIRICK, G. S., THOMAS, L., and ZIEGLER, J. E., JR.: A virus recovered from patients with primary atypical pneumonia, *Science*, 1943, xcvi, 289-291.
13. EATON, M. D., MEIKLEJOHN, G., and VAN HERICK, W.: Studies on the etiology of primary atypical pneumonia. A filterable agent transmissible to cotton rats, hamsters and chick embryos, *Jr. Exper. Med.*, 1944, lxxix, 649-668.
14. HORSTMAN, D. M., and TATLOCK, H.: Cold agglutinins. A diagnostic aid in certain types of primary atypical pneumonia, *Jr. Am. Med. Assoc.*, 1943, cxxii, 369-370.
15. TURNER, J. C., NISNEWITZ, S., JACKSON, E. B., and BERNEY, R.: Relation of cold agglutinins to atypical pneumonia, *Lancet*, 1943, i, 765-769.
16. MEIKLEJOHN, G.: The cold agglutination test in the diagnosis of primary atypical pneumonia, *Proc. Soc. Exper. Biol. and Med.*, 1943, liv, 181-184.
17. Commission on Acute Respiratory Diseases: Cold hemagglutinins in primary atypical pneumonia and other respiratory infections, *Am. Jr. Med. Sci.*, 1944, ccviii, 742-750.
18. HEINTZELMAN, J. H. L., and SELIGMANN, A. W.: Evaluation of the cold agglutination test in primary atypical pneumonia, *U. S. Nav. Med. Bull.*, 1944, xliii, 433-437.
19. HUMPHREY, A. A.: Cold hemagglutination test in diagnosis of primary atypical pneumonia, *U. S. Nav. Med. Bull.*, 1944, xliii, 1117-1127.
20. FETTERMAN, G. H., MORAN, T. J., and HESS, W. R.: The cold agglutination test, *U. S. Nav. Med. Bull.*, 1944, xliii, 1128-1136.
21. FAVOUR, C. B.: Autohemagglutinins—"Cold agglutinins," *Jr. Clin. Invest.*, 1944, xxiii, 891-897.
22. STREETER, G. A., FARMER, T. W., and HAYES, G. S.: Cold hemagglutination in primary atypical pneumonia, *Bull. Johns Hopkins Hosp.*, 1944, lxxv, 60-66.
23. FINLAND, M., PETERSON, O. L., ALLEN, H. E., SAMPER, B. A., BARNES, M. W., and STONE, M. B.: Cold agglutinins. I. Occurrence of cold isohemagglutinins in various conditions, *Jr. Clin. Invest.*, 1945, xxiv, 451-473.
24. MEIKLEJOHN, G., EATON, M. D., and VAN HERICK, W.: A clinical report on cases of primary atypical pneumonia caused by a new virus, *Jr. Clin. Invest.*, 1945, xxiv, 241-250.
25. MEIKLEJOHN, G., and HANFORD, V. L.: Agglutination tests with streptococcus No. 344 in primary atypical pneumonia, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvii, 356-358.
26. FINLAND, M., SAMPER, B. A., and BARNES, M. W.: Cold agglutinins. VI. Agglutinins for an indifferent streptococcus in primary atypical pneumonia and in other conditions and their relation to cold isohemagglutinins, *Jr. Clin. Invest.*, 1945, xxiv, 497-502.
27. EATON, M. D.: Serological differentiation of primary atypical pneumonia from virus pneumonia of the psittacosis group, *Proc. Soc. Exper. Biol. and Med.*, 1945, lx, 231-235.
28. EATON, M. D., and VAN HERICK, W.: Serological and epidemiological studies on primary atypical pneumonia and related acute upper respiratory disease, *Am. Jr. Hyg.*, 1947, xlv, 82-95.
29. Commission on Acute Respiratory Diseases: The transmission of primary atypical pneumonia to human volunteers, *Bull. Johns Hopkins Hosp.*, 1946, lxxix, 97-167.



# THE GENESIS OF THE NEUROSES\*

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THE Second World War focused much attention upon the psychoneuroses, and to many the fact that over a million of our young men were not fit for military service because of psychoneuroses was a jolt. Much has been written about the rôle of the war in the production of the psychoneuroses—but military service did little more than act as the precipitating factor, since almost as many young men were rejected for service as were dismissed from the armed forces because of neurotic disorders. Psychoneurotic illness has always been with us, and I do not believe it will ever be eliminated as a major cause of discomfort and disability.

Before proceeding to any discussion of a disease it is well to define it, though the difficulties of presenting an entirely satisfactory definition will be appreciated. To me a psychoneurosis is a group of symptoms which may be physical, mental, or both, which develop in an individual when he is incapable of dealing successfully with the circumstances in his life at a given time. His powers of adaptability are inadequate in the face of the complexities of the present situation. There are two implications in this definition of which I hope you will make note: first, that neuroses occur in response to demands made upon the individual. These demands may come from without or from within the person. Secondly, observe that this definition implies that recovery from a neurosis is possible. Improvement may be brought about either by reduction of the demands upon the individual or by the acquisition of additional knowledge and understanding, by which his ability to adjust or cope with the situation is improved. The former method is exemplified by the regimen which requires a long rest "getting away from it all," or some other procedure which masks the situation or otherwise diminishes the pressure. The latter method is best illustrated by a program of psychotherapy which increases the person's adaptive powers.

Before discussing the genesis of neuroses I would like to recall an old facetious comment that "Life is a funny proposition; man is born into this world without his consent, leaves it against his will, and finds the voyage between exceedingly rough." The fact that life has been more onerous for some persons than others explains why some develop personality and adjustment difficulties while others are much better adjusted. In considering what the real difficulties of life are we are inclined, because of our training as physicians and the dominance which pathology has held over us, to think in

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terms of material things; consequently an individual's environment is frequently evaluated by whether or not he has known poverty or whether his family has been successful, respectable and intelligent. When the answer to these questions is favorable we often hear expressions of mystification that the son or daughter of such a family can be such a misfit. Let this attitude be improved by appreciating that "man does not live by bread alone."

Recent advances in psychiatry have led to an appreciation of the fact that we have been prone to ignore the experiences of early years, and the rôle they may play in the production of psychoneuroses. Freud and his followers have successfully and wisely focused attention on the early experiences in life. We recognize that the span of life within our memory has been one in which there has been considerable conflict, but forget that the period beyond our recall may be even more difficult. Immediately upon our arrival in this world we begin to experience new sensations, and soon have restraints placed upon us as we endeavor to gratify the instinctive drives which assert themselves. By the time we become aware of the nature of social restraints we try to adapt our actions and thinking so we will attain gratification in a form and under circumstances approved by society, of which we aim to become an acceptable member. We are constantly striving toward a better integration with the society in which we live, to try to find purpose in our existence, with gratification of our inward drives in such a way that we acquire satisfactory self-esteem. In our drive toward maturity we strive to arrive at a hetero-sexual adjustment, find an appropriate love object of the opposite sex, live in harmony with the members of our family and society, and abide by their customs and dictates. The individual who attains these objectives we may regard as one who is mature.

Briefly let us consider life from its beginning. After conception a time arrives when the embryo develops to the point where it is capable of consciousness of its own existence. The in utero existence of the individual is rather an idyllic one in which all the bodily needs are taken care of by the host, the mother. It lives in a water cushion, protected from injury in a most satisfactory way. As the time of gestation approaches its termination the unborn undergoes some new and unpleasant experiences as the preliminary contractions of the uterus arouse consciousness to the point of appreciating uncomfortable sensations. As these contractions become the labor contractions its previous state of tranquillity is disturbed as it is squeezed and forced into the birth canal. Reflexly it participates in its own birth by attempts at extension of its body, forcing itself downward through the canal, and eventually as it arrives in this world, nearly in a state of exhaustion, it is suddenly projected into our midst. After some harsh manipulation including a few spans on the back, the infant breaks into his first cry which I believe is one of protest rather than elation. Soon after voicing his resentment he falls asleep, a state of diminished consciousness which resembles that in which he previously existed in utero. He awakens to be assailed by

new sensations, among them being hunger as well as irritation at the swaddling clothes which are not as comforting to his skin as was the amniotic liquid. He is nursed; he falls asleep, and as this process repeats itself he soon begins to appreciate the pleasant experience of suckling, of having nice warm food enter his stomach and agreeably end the uncomfortable sensation of hunger. At the time he is held to the breast he experiences the external warmth of the mother's body and her fondling, and wishes its repetition. He rejects the unpleasant sensations of hunger, cold, noise and many others that occur to him in early life. Among the things he may find unpleasant and reject is noise, including the booming voice of the father as well as his rough manipulations. When pleasant and comforting experiences are provided in abundance we will have the happy, contented, well behaved infant off to a good start, but he may still experience mismanagement in later infancy with resulting frustration and deviation into a neurotic pattern.

As the infant lives out the early months of life and becomes aware of his existence he soon appreciates that he has and knows comfort through the bounty of persons outside himself. He is utterly dependent, and when those upon whom he depends fail to meet or anticipate his needs, he may experience anxiety or fear. When the gratification of his needs is suddenly interrupted he may often be noted to respond with obvious anger. A few months ago I was visiting at the home of young friends as the mother was nursing her two month old son. A caller necessitated the brief interruption of the nursing of the baby. As the infant was laid upon a couch he gave a beautiful demonstration of absolute rage, and when the mother returned to the nursing she was forced to wince in response to his angry bites of protest. So, to any observer, emotion may be detected in the early weeks of life. The absolute state of dependency is gradually eliminated as the child acquires new powers, e.g., the ability to move and thereby get away from unpleasant situations, or through movement to create pleasant sensations. Hence we have observed many youngsters roll their heads and flap their extremities in great glee as they experience the new power of control over their muscles and the exhilarating sensations of self-desired movements.

In a short presentation it is impossible to continue the visualization of this hypothetical child through the various stages of his development, but soon, because of his newly acquired power to move about, it is necessary to exercise restraint and supply guidance. This usually falls to the lot of the mother to whom the child is strongly attached; if she is kindly, patient, and intelligent, and endeavors to transmit to the child her reasons for the restraint the child suffers a minimal amount of anxiety, but when he is subjected to harsh and inconsiderate methods his anxieties may become almost overwhelming. Society, through the mother or mother-surrogate, is constantly endeavoring to mold the child into a pattern of acceptable behavior, and one of the demands of society is that of bodily cleanliness. Consequently

toilet-training is essential but it should never be begun until the child is entirely capable of appreciating the need of cleanliness. There has been no greater absurdity than the tendency of the pediatrician to begin toilet training at the age of one or two months. If the child is led and directed rather than coerced, and receives in exchange for his own efforts some reward and increase in his self-esteem he gradually acquires toilet-training as he does other acceptable traits. However, when he is coerced he may, because of his resentment, retard toilet-training accomplishments to a late date as one of the most satisfactory ways of expressing his resentment and hostility toward the mother or mother-surrogate. An effort should be made not to force upon a child a pattern of behavior for which he is not ready. Do not demand more adult performance than that of which he is capable.

Before we progress further I would like to speak of the importance of the atmosphere in the home that is created by the parents. If it is one of peace and tranquillity it is one in which the handling of the child will assuredly be considerate. But if the home atmosphere is filled with bickering and a great deal of tension, the child soon begins to respond with manifestations of fear. I would like to speak very briefly of a child under my observation almost from the time of birth although only as a "friend of the family." The mother was well known to me as a youngster prone to outbursts of terror at the sight of a horse, dog or some strange object. She was also given to outbursts of temper and breath-holding, which demonstrations of fear and anxiety "according to the neighbors" made her own mother a nervous wreck. I was present on one occasion when after becoming a mother she was nursing her firstborn child, then about two months old. The quiet was suddenly shattered by the backfiring of a truck, whereupon the mother jumped; the breast fell out of the child's mouth, and immediately he showed absolute terror as he was almost dropped from the mother's arms. I do not consider this incident a determining factor in the child's life. However, I had the opportunity of observing the same child shortly after he was two years old when as strangers entered the room he jumped from the mother's lap and hid behind a chair. Then a dog belonging to the newcomers came into the room suddenly, whereupon the child scrambled into his mother's lap with a scream. As the dog rushed forward to investigate the noise, the mother joined the child in the screaming, and in far less time than it has taken me to tell you of it the child began to vomit down the mother's back; the mother fainted and required restoratives. The two year old child was distinctly a neurotic; call the mother what you wish. I have been informed by those who have known the child all through his life that he has vomited whenever the slightest event occurred creating noise, tension or anxiety in the household.

I am sure many of you are already disappointed and possibly are feeling anxiety because I have not mentioned that which some of you have been led to believe is the principal cause of all neurotic disturbances, namely, sex.

I am certain that this attitude—of sex being so largely responsible for neurotic behavior—is one that has become established as a result of the fly-by-night adherents of Freud who have disseminated inadequate understanding of his principles. At any rate it has been the experience of psychiatrists to discover that most physicians regard sex as of tremendous importance in the genesis of the neuroses. Not only is it considered the principal cause but many are prone to regard sex relations as a most beneficial therapeutic procedure. It is not unusual to see patients who have been advised to marry in order to recover from their neuroses, or worse yet, advised to seek sex experiences as a therapeutic measure. Sex, as a therapeutic measure, is the only thing I know which may be more over-rated than Southern cooking.

The sex instinct is basically a drive for love. As I have already indicated, the child's first love is the love of his mother because she means so much to his well-being. He naturally is anxious to retain that love for himself, and when he sees the father in a rival rôle for the time and affection of the mother it may be the source of infantile anxiety. It is not at all unusual to hear a child express the intention of shooting his father and marrying his mother when he is grown up. You may have observed it in your own experience. As the child broadens his field of activities he strives for the affection of others and for manifestations of their approval. By such experiences and the incident rivalries the child acquires knowledge and improves his adaptive powers. As this occurs he becomes less dependent upon the mother, and some of his desires for affection and love are gratified by his experiences with other children. Little boys and girls at the age of six or seven are devotedly attached to each other and derive from each other a great deal of gratification. It is inevitable during this time and even earlier that boys will discover their sex organ; it is during this period that sex play between children is going to develop since it is motivated by curiosity, and during this time of life one of the major trauma occurs. First of all the mother may wish to retain the affection of the child permanently; she scolds him because he has reached a point where he likes to spend more time with the children next door than with her, etc. It is also a time when mothers discover the tendency of their children toward sex play and their desire to acquire understanding of sex, and mothers often rebuke children or fail to give them proper answers and so behave that they build up strong feelings of guilt around matters of sex. Then there comes a time when society separates children according to sex; this is definitely a period of homosexual attachment. It is axiomatic that if one has not learned simple arithmetic, such as the multiplication tables, one cannot progress to a satisfactory understanding of long division or algebra. So the child who has not had the opportunity of passing through these various phases of emotional development cannot become competent in the more intricate pattern of adult living. As a consequence a heterosexual adjustment may be difficult or impossible

to achieve. It is our failure to appreciate that the sex urge is basically a drive for the affection of desirable individuals; that it is essentially innocent and without guilt until our culture makes it so, that impairs the ability to adjust satisfactorily. Much has been written about the giving of sex information to children, and we can only generalize by saying that when a child asks questions about sex the parent should give a simple, honest answer to satisfy the child's need at that moment. Parents must not act as though it was something which made them very uncomfortable, for by such attitudes they may raise anxiety in the child's mind. Then in the future the youngster will avoid asking any questions, and the parents will have lost the golden opportunity of participating in their child's development.

I would like to speak of one other strong instinct and comment on the handling of it in society. We all know the child has a strong self-acquisitive instinct, and in early life we are all guilty of many acts of petty thievery. This instinct, like that of sex, never leaves us; as we grow older we still have the "Gimmies" and "I wants," but very few of us, if any, are thieves because our mothers, who understand that children are going to steal a little bit, are patient, and eventually they carefully point out to children the property rights of other individuals. Ultimately, the child learns that there are proper and improper ways of acquiring property, and to follow the accepted way becomes essential because the approving attitude of others does help to develop our self-esteem. If a similarly intelligent, patient, and consistently applied attitude could be adopted toward sex, anxieties about sex would be no more disturbing than the fact that when we do not make as much money or have as much of the world's goods as we would like to have we do not feel guilty but exert efforts to gratify our acquisitive instinct through increased effort.

In this short presentation I have tried to focus attention upon the importance of the very earliest weeks and months of life in the eventual formation of personality. I have tried especially to indicate that the love life of the child begins with his attachment to the mother, that it progresses through attachment to other individuals, especially to children, and passes through a period of strong homosexual attachment before it arrives at a final heterosexual adjustment. At this point I would like to indicate that a heterosexual adjustment does not imply that to be adjusted adequately at the heterosexual level an individual must have sex relations.

If during any of the periods of growth the child does not experience normal gratification and is not afforded satisfactory opportunity for development and adjustment, a neurotic pattern may be established. The pattern may continue throughout life or may be improved as a result of favorable influences. In the latter instances some deficiency may remain and in later life, under difficult circumstances, the pattern of neurotic behavior may again assert itself.

Before closing I would like to speak briefly of measures which I feel can contribute to the prevention of many psychoneurotic and maladjusted per-

sons. The etiology of the neuroses is now rather well understood, though there are many gaps to be filled in the knowledge which we possess. With the knowledge we do have, the psychiatrist is capable of effecting a cure in a large percentage of patients, and from this experience we are gradually evolving methods for the prevention of neuroses. As with every true physician, efforts toward prevention must be intensified by the psychiatrist to serve the public best. As knowledge of the prevention of physical illness has increased, mothers have shown an intense interest and have endeavored to avail themselves of all prophylactic measures. Their knowledge of the dietetics of infancy has diminished infant dysentery, and other gastrointestinal disturbances. These same mothers are just as anxious to have made available to them knowledge which will enable them to rear more satisfactorily adjusted children. Because of this I feel the psychiatrist must make available to these mothers that knowledge which will be helpful, through integrating their services with the prenatal and well-baby clinics. The general practitioner and pediatrician must become better informed and more capable of acting as advisers to mothers on matters pertinent to the emotional development of infants and children.

# CASE REPORTS

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## THE ETIOLOGY OF BANTI'S SYNDROME; FURTHER SUPPORT OF THE "CONGESTIVE SPLENOMEGALY" HYPOTHESIS \*

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BANTI, in describing the syndrome which bears his name, attributed the condition to an unknown toxin acting primarily on the spleen. This concept was questioned as early as 1904 by Dock and Warthin,<sup>1</sup> who described two cases of Banti's syndrome associated with stenosis and calcification of the portal vein. These investigators believed that the histological changes in the spleens of these cases could be explained by prolonged passive congestion and suggested the possibility that the clinical picture might be caused by portal vein stenosis. Subsequently Dürr<sup>2</sup> observed that sections of the spleens from Banti's original cases showed pathological changes indistinguishable from those found in the spleen in cases of cirrhosis of the liver. Warthin<sup>3</sup> reviewed many cases of Banti's syndrome and concluded that in at least some cases the condition was a result of portal or splenic vein obstruction. Larrabee<sup>4</sup> studied the records of 47 cases of the disease and was "forced to the conclusion that most if not all of these cases were not only associated with lesions interfering with the outflow of blood from the spleen, but were actually the results of such lesions."

The "congestive" theory of the pathogenesis of Banti's syndrome has been given very strong support by the recent clinical and experimental studies in the Spleen Clinic of the Presbyterian Hospital in New York.<sup>5, 6, 7, 8</sup> It appears that the syndrome characterized by splenomegaly, anemia, leukopenia and increased collateral circulation between the portal and systemic venous beds is the usual result of splenic vein hypertension. Cirrhosis of the liver, formerly looked upon as a regular feature of Banti's syndrome, is now recognized as etiological in some cases because of the portal hypertension which it produces. However, in cases in which portal obstruction is extra-hepatic, cirrhosis does not occur.<sup>8</sup> Many cases of Banti's disease have now been described in which a variety of obstructive factors have been demonstrated, including cirrhosis of the liver, thrombosis of the splenic or portal vein, cavernomatous transformation of the portal vein and portal stenosis. The clinical and pathological studies which have already been made would seem to leave little doubt as to the veracity of the "congestive" etiology of Banti's syndrome. Nevertheless, there are still some, e.g. Ravenna,<sup>9</sup> who are unwilling to accept this evidence and it is for this reason that the present case is reported.

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From the AAF Regional Hospital, Maxwell Field, Alabama.



## CASE REPORT

A 33 year old white housewife was admitted to the hospital on December 11, 1944 because of hematemesis starting six hours prior to admission. The family history was non-contributory. The patient was born and had always lived in Alabama. She had been married for four years but had no children. Before the onset of her present illness she had had no important sickness. She smoked an occasional cigarette but never used alcohol. She denied having taken drugs or having been exposed to any toxic agents.

She stated that she had been in excellent health until 1936 when at the age of 25 she suddenly and without antecedent symptoms had a large hematemesis. She was admitted to a hospital where she was told that she had an ulcer of the stomach. She was placed on a strict ulcer regimen but the gastric hemorrhage persisted and was controlled with great difficulty. After the cessation of bleeding she became asymptomatic. However, following this occurrence she had similar severe hematemeses once or twice a year. In the interval between bleeding episodes she felt quite well with no gastrointestinal or other symptoms. She had never had jaundice or ascites.

About one year before admission she had two episodes of very severe hematemesis within three months. Therefore, in January 1944 she was admitted to another hospital where she was studied and a splenectomy was performed. She was told that her liver appeared normal. She had an uncomplicated recovery from the operation and remained in good health until the day of admission to this hospital. About six hours before admission she began to feel faint and dizzy. She then became nauseated and vomited about a half-pint of bright red blood. Several hours later she vomited about an equal quantity of dark blood. She was then brought to the hospital.

On admission she was ambulatory and in no acute distress. She was pale but well developed and well nourished and did not appear to be very ill. Temperature was 98° F., pulse 88, respirations 20 and blood pressure 102 mm. of mercury systolic and 55 diastolic. Aside from pallor the skin and mucous membranes were clear with no spider angiomas, edema, or jaundice. There were no dilated veins visible on the thorax or abdomen. Examination of the head and neck was not remarkable. The heart and lungs were normal. There was a healed midline upper abdominal scar. The abdomen was soft and not tender. There was no evidence of free fluid. The liver was not palpable nor were any other organs or masses felt. The remainder of the physical examination was negative. Red blood count on admission was 4,200,000, hemoglobin 12.3 grams (84 per cent), white count 19,200 and platelet count 260,000.

She was given morphine but shortly after admission again vomited a large quantity of blood. Thereafter hematemeses were frequent and severe. She was repeatedly transfused but it was not possible to replace the blood as rapidly as she lost it. In less than 24 hours after admission she died of hemorrhagic shock.

Blood was drawn for chemical tests about eight hours after admission. The persistent hemorrhage and repeated transfusions make the results of some of these tests of little significance. Non-protein nitrogen was 29 mg. per cent, cholesterol 214, bilirubin 1.1, phosphorus 2.4, phosphatase 2.6 Bodansky units, total protein 5.3 per cent, albumin 2.8 per cent and globulin 2.5 per cent. Cephalin flocculation was two plus and sedimentation rate 24 mm. in one hour.

It was felt that this patient did not have cirrhosis. There was no history of alcoholism and there was nothing in the history or physical findings which suggested liver disease. Furthermore, she had been told following splenectomy that her liver appeared normal. Therefore, we believed that her Banti's syndrome was caused by an extrahepatic obstruction of the portal circulation. The clinical examination gave no clue as to the nature of this obstruction. The clinical diagnosis was Banti's syndrome secondary to extrahepatic portal obstruction of unknown nature with death resulting from rupture of esophageal varices.

At autopsy the significant findings were limited to the abdomen. The peritoneal cavity contained no free fluid. The liver weighed 1160 grams and appeared to be normal. The spleen had been removed, but in the splenic bed, coursing over the pancreas, were numerous tortuous, greatly dilated veins establishing collateral circulation between the splenic vein and the veins of the stomach. The branches of the portal system were enlarged and the portal vein itself was dilated. A careful dissection of the portal vein revealed that just as it entered the liver the vein was thrown into a sharp "S" turn and its lumen was reduced to about 2 mm. Beyond this constriction the vein terminated abruptly in a small saccular dilatation from which several minute branches extended into the right lobe of the liver. These branches were so small that they would hardly admit the end of a probe. No branch to the left lobe of the liver could be demonstrated. There was no evidence of scarring or thickening of the almost blind end of the portal vein and the intimal surface appeared to be normal. It was apparent that very little portal blood could have entered the liver through this anomalous vein. Microscopic examination revealed no abnormality of the liver except in one small area where there was a focal collection of small round cells. There was no evidence of cirrhosis. The stomach was distended, containing about 1500 c.c. of fresh blood. In the posterior wall of the cardia 1.5 cm. below the esophageal junction were three elevated ridges running in the long axis of the stomach and having the gross appearance of rugae. At the esophageal end of the largest of these was a punched-out purplish erosion 2 mm. in diameter. On section the longitudinal folds were seen to be produced by large varices within the wall of the stomach. The eroded area in the gastric mucosa opened into one of these vessels and was the source of the fatal hemorrhage. The abdominal viscera were otherwise normal except for dilatation of the venous channels in the submucosa of the gastrointestinal tract.

Subsequently a report was obtained from the hospital in which the patient had had her splenectomy. The records showed that on admission to that hospital in January 1944 physical examination had revealed an enlarged spleen. The liver was not palpable and there were no other significant physical findings. Laboratory studies done at that time included a red cell count of 3,520,000, hemoglobin 59 per cent, white cell count 2400 with normal differential count, and platelet count 144,000. Bleeding and clotting time and a red cell fragility test were normal. Sternal marrow biopsy showed no abnormalities except that the marrow was perhaps slightly hyperplastic. She was considered to have Banti's disease and a splenectomy was performed. The spleen was adherent to the omentum, diaphragm and adjacent peritoneal surfaces. There were tremendous veins as large as a finger running into the spleen from every side. The liver appeared to be normal. The spleen weighed 550 grams. The capsule was thickened and on section the organ showed a notable increase in fibrous tissue. The Malpighian bodies appeared compressed and reduced in number. Perivascular fibrosis was most prominent around the veins. The findings were considered to be consistent with a long standing passive congestion corresponding to the morphological picture seen in Banti's disease.

### DISCUSSION

This case is reported in further support of the "congestive" hypothesis of the pathogenesis of Banti's syndrome. A number of very similar cases have previously been described,<sup>5</sup> in which the cause of the splenic vein hypertension was an extra-hepatic obstruction of the portal or splenic vein. Ravenna<sup>2</sup> believes that the finding of such lesions as thrombosis, stenosis or cavernomatous transformation of the portal vein does not prove the congestive etiology of Banti's disease and thinks that these lesions are secondary to a primary disease

of the spleen. A significant feature of the present case is that the obstructive lesion was unquestionably a congenital anomaly and therefore the primary cause of the portal hypertension. We believe that the age to which our patient lived before her first hematemesis is quite remarkable in view of the nature of her lesion.

Congenital anomalies of the portal vein producing portal hypertension are apparently rare although they have been previously described.<sup>10, 11</sup> Thompson<sup>7</sup> reported a small group of cases in which the obstructive factor was thought to be an anatomical defect or thrombosis of the portal vein occurring at or before birth, but the exact nature of the lesion was not proved in his cases. Perhaps a more careful search for such anomalies at autopsy in young individuals dying with the Banti type of picture might reveal a higher incidence of such lesions.

In this regard, an important feature of the present case is the difficulty with which the obstructive lesion was demonstrated. It would have been absolutely impossible to have found the obstruction at operation, even with the most careful exploration. At autopsy the lesion almost certainly would have been overlooked had it not been painstakingly sought. The portal vein appeared dilated but otherwise normal as it entered the liver and its almost blind-end termination was discovered only when its course was traced into the liver substance. Warthin<sup>3</sup> commented on the relatively large number of cases of splenic anemia reported without mention of portal or splenic vein obstruction and pointed out that these veins are not thoroughly examined at the usual autopsy. In this connection the case of Trimble and Hill<sup>12</sup> is of interest. These authors described a patient with Banti's syndrome in whom a stenosis of the portal vein was overlooked at autopsy. This important lesion was found only on reexamination of the specimen after attention was called to the significance of such an examination.

As in previously reported cases of extra-hepatic portal obstruction, the liver in our patient was normal in spite of the very long duration of the portal obstruction. This finding again confirms the belief expressed by Thompson<sup>7</sup> that cirrhosis occurs in Banti's disease only when it is present as the obstructive mechanism.

In view of our present knowledge a diagnosis of "Banti's disease" is no longer adequate. In every such case the underlying pathogenetic lesion should be sought. This is particularly important since the advent of new therapeutic technics. To some extent the prognosis and treatment of the condition depends upon the nature of the causative lesion. Splenectomy in all cases tends to cause the blood picture to return to normal. The anemia, leukopenia and thrombocytopenia appear to be a direct result of the presence of the congested spleen and usually disappear following its removal. Furthermore, splenectomy may reduce the volume of the portal circulation and thus relieve some of the burden placed upon the collateral circulation. When the obstructive lesion is limited to the splenic vein splenectomy may be curative. New procedures in vascular surgery by which portal-caval shunts may be produced may offer hope of prolonged life to patients with portal hypertension.<sup>13</sup> When the obstructive lesion is a disease process such as cirrhosis, the underlying disease should be treated. As with other disease processes, intelligent treatment requires an understanding of the disordered function.

## CONCLUSIONS

1. A case of Banti's syndrome is described in which the causative lesion was a congenital obstruction of the portal vein at its termination within the substance of the liver.

2. This case is offered as further evidence in support of the "congestive" origin of Banti's syndrome and is thought to be of special significance because of the congenital and therefore obviously primary nature of the obstructive lesion.

3. The difficulty in demonstrating the obstructive lesion in this case again emphasizes the importance of very careful exploration of the portal and splenic veins at autopsy in all cases of Banti's syndrome.

## BIBLIOGRAPHY

1. DOCK, G., and WARTHIN, A. S.: A clinical and pathological study of two cases of splenic anemia, with early and late stages of cirrhosis, *Am. Jr. Med. Sci.*, 1904, cxxvii, 24-55.
2. DÜRR, R.: Bantimilz und hepatolienale Fibrose, *Beitr. z. path. Anat. u. allg. Path.*, 1924, lxxii, 418-455.
3. WARTHIN, A. S.: The relation of thrombophlebitis of the portal and splenic veins to splenic anemia and Banti's disease, *Internat. Clin.*, 1910, iv, 189-226.
4. LARRABEE, R. C.: Chronic congestive splenomegaly and its relationship to Banti's disease, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 745-760.
5. ROUSSELOT, L. M.: Congestive splenomegaly (Banti's syndrome), *Bull. N. Y. Acad. Med.*, 1939, xv, 188-196.
6. ROUSSELOT, L. M., and THOMPSON, W. P.: Experimental production of congestive splenomegaly, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 705-708.
7. THOMPSON, W. P.: The pathogenesis of Banti's disease, *Ann. Int. Med.*, 1940, xiv, 255-262.
8. ROUSSELOT, L. M.: The late phase of congestive splenomegaly (Banti's syndrome) with hematemesis but without cirrhosis of the liver, *Surgery*, 1940, viii, 34-42.
9. RAVENNA, P.: Splenoportal venous obstruction without splenomegaly, *Arch. Int. Med.*, 1943, lxxii, 786-794.
10. SCHRANK, A.: Ein seltener Fall von abnormer Pfortaderverengung und -aufspaltung, *Klin. Wchnschr.*, 1940, xix, 1217-1218.
11. FRASER, J., and BROWN, A. K.: A clinical syndrome associated with a rare anomaly of the vena portae system, *Surg., Gynec. and Obst.*, 1944, lxxviii, 520-524.
12. TRIMBLE, W. K., and HILL, J. H.: Congestive splenomegaly (Banti's disease) due to portal stenosis without hepatic cirrhosis; aneurysms of the splenic artery, *Arch. Path.*, 1942, xxxiv, 423-430.
13. BLAKEMORE, A. H., and LORD, J. W.: A non-suture method of blood vessel anastomosis, *Jr. Am. Med. Assoc.*, 1945, cxxvii, 748-753.

## PRIMARY SPLENIC HODGKIN'S DISEASE WITHOUT LYMPH NODE INVOLVEMENT \*

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IN 1832 Hodgkin<sup>1</sup> called attention to the existence of a disease characterized by progressive enlargement of the lymph nodes and associated in many instances with enlargement of the spleen. Seventy-five years later Reed<sup>2</sup> stated "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis in which the disease commenced elsewhere than in the lymph nodes." Even today most medical authors deny the existence of a primary splenic form of the disease.

Symmers,<sup>3</sup> however, in 1909 described a case of an 18 year old girl with recurrent chills and fever and a progressively enlarging spleen. The pathological picture in the spleen removed at operation was typical of Hodgkin's disease. No superficial lymph nodes were palpable and no enlarged nodes were found in the abdomen at operation. The patient died soon after operation, but unfortunately necropsy was not done. Hence examination of the mediastinal nodes, a frequent site of involvement, was not possible. The same criticism can be made for Wade's<sup>4</sup> and Dowd's<sup>5</sup> cases in which splenectomy alone was performed.

The first authentic report of a primary splenic form of the disease was by Krumbhaar<sup>6</sup> in 1931 in which there was extensive involvement of the spleen and bone marrow at autopsy, but no evidence of Hodgkin's disease in any of the lymph nodes. Similar cases were reported by Sears and Black<sup>7</sup> in which the thymus was also involved, and by Bordoni-Possi, Rurriel, and Ardao<sup>8</sup> in which the spleen alone showed the typical Hodgkin's picture. No bone marrow studies were done in the latter case. Finally, Gebauer<sup>9</sup> described a case with isolated involvement of spleen and bone marrow in which an antemortem diagnosis was made.

### CASE REPORT

B. P., a 62 year old white male, was first admitted to The Jewish Hospital of Brooklyn on September 28, 1945 complaining of swelling of the ankles of six to eight weeks' duration and exertional dyspnea for the same period of time. For the past 10 years he had been unable to work because of severe weakness. He was occasionally told he was "yellow" in the last six months and had lost 25 pounds in weight during the last year. He had been accustomed to drinking four to five glasses of whiskey a day until 10 years before admission but drank only occasionally since then.

The positive findings on admission were a nodular liver palpable three fingers' breadth below the right costal margin and a spleen palpable four fingers' breadth below the left costal margin. There was also brawny non-pitting edema of both ankles. His blood count at this time showed a hemoglobin of 34 per cent, a red blood count of 1.98 million per cu. mm., a white blood count of 2209 with 40 per cent polymorphonuclears, 2 per cent bands, 55 per cent lymphocytes, and 3 per cent monocytes. The smear showed anisocytosis, and basophilic stippling with 30 normoblasts. Bone marrow studies showed many "smudge" forms. There was no

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From the Department of Laboratories, Jewish Hospital of Brooklyn.

evidence of erythroblastosis. Roentgen-ray examination of the esophagus showed no evidence of varicosities. Studies of the lower femora (Gaucher's disease was suspected) showed only bilateral phlebosclerosis. Except for a cephalin flocculation of 4+ the liver function tests and all blood chemistries were within normal limits. The red cell fragility was normal.

A diagnosis of Laennec's cirrhosis was made and the patient was treated with vitamins, crude liver extract and blood transfusions and discharged October 31, 1945 when his hemoglobin had been raised to 51 per cent and he felt improved.



FIG. 1. Photograph of spleen showing fibrosis and an infarct in the lower pole.

He was readmitted on December 4, 1945 complaining of weakness, loss of appetite, shortness of breath and sharp pain in the left upper quadrant on coughing or deep breathing. He had lost 5 lbs. in the 10 days before admission. The liver was now palpable 5 cm. below the right costal margin and was not nodular. The spleen was estimated to be three times normal size. The blood and bone marrow pictures and blood chemistries remained unchanged. He was again treated with vitamins and crude liver extract and discharged December 30, 1945 subjectively improved.

His final admission was on January 7, 1946 when he entered complaining of chills and fever and pain in the right chest for four days. His lips were cyanotic and his skin yellow-tinged. He had wheezing respirations throughout the chest, moist râles at both bases, diminished breath sounds and dullness at the right base. There was a blowing systolic murmur at the apex of the heart. The liver and spleen were both palpable four fingers' breadth below the costal margins. The liver was not nodular.

The blood count showed a hemoglobin of 32 per cent, red blood count 1.56 million, white blood count 4100 with 2 per cent polymorphonuclears, 8 per cent bands, 86 per cent lymphocytes, and 4 per cent monocytes. Despite vitamins, massive doses of penicillin and digitalis the patient went rapidly downward and died on January 11, 1946.

*Autopsy:* At postmortem examination done four hours after death, the body was that of a well developed and well nourished white male measuring 157 cm. in length.

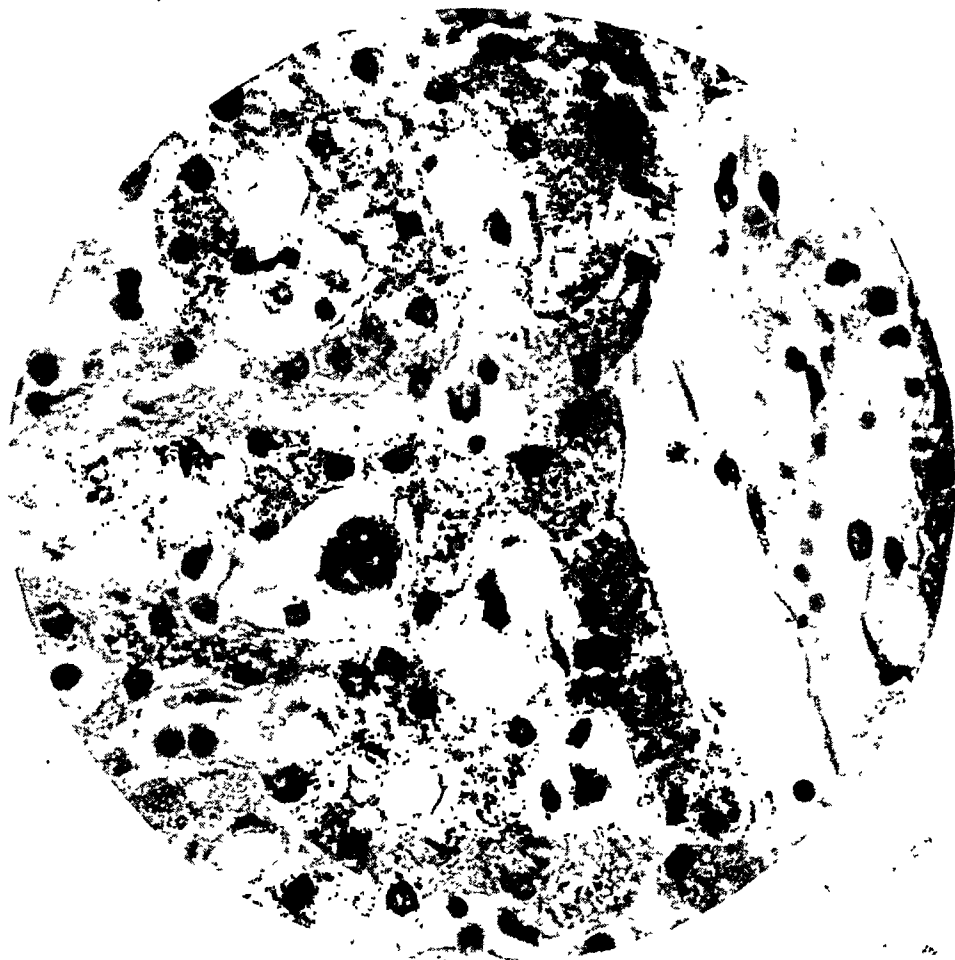


FIG. 2. Photomicrograph of liver showing pigmentation of liver cells and large cells in sinusoids. H & E  $\times 320$ .

No external lymphadenopathy was present. The skin and sclerae showed a faint yellow tinge and there was a 2+ brawny non-pitting edema of both ankles. There were 200 c.c. of clear yellow fluid in the peritoneal cavity and firm adhesions at the apices of both lungs.

**Heart and Aorta:** The heart was of normal size and showed some white streaking in the left ventricle near the septum.

**Respiratory System:** The entire right lung was firm and rubbery in consistency. On section the parenchyma was pink gray and non-crepitant. The left lung was crepitant and emphysematous. Both pleurae were roughened by fibrous adhesions near the apices.

**Liver and Biliary System:** The liver weighed 2,655 gm. and measured 32 by 24 by 7.5 cm. The external surface was red brown, smooth and glistening and on section the lobular pattern was somewhat accentuated. The portal vein contained no thrombi. The gall-bladder was contracted and contained a large smooth oval-shaped golden yellow calculus measuring 2 cm. in greatest diameter.

**Pancreas and Adrenals:** These showed nothing of note.

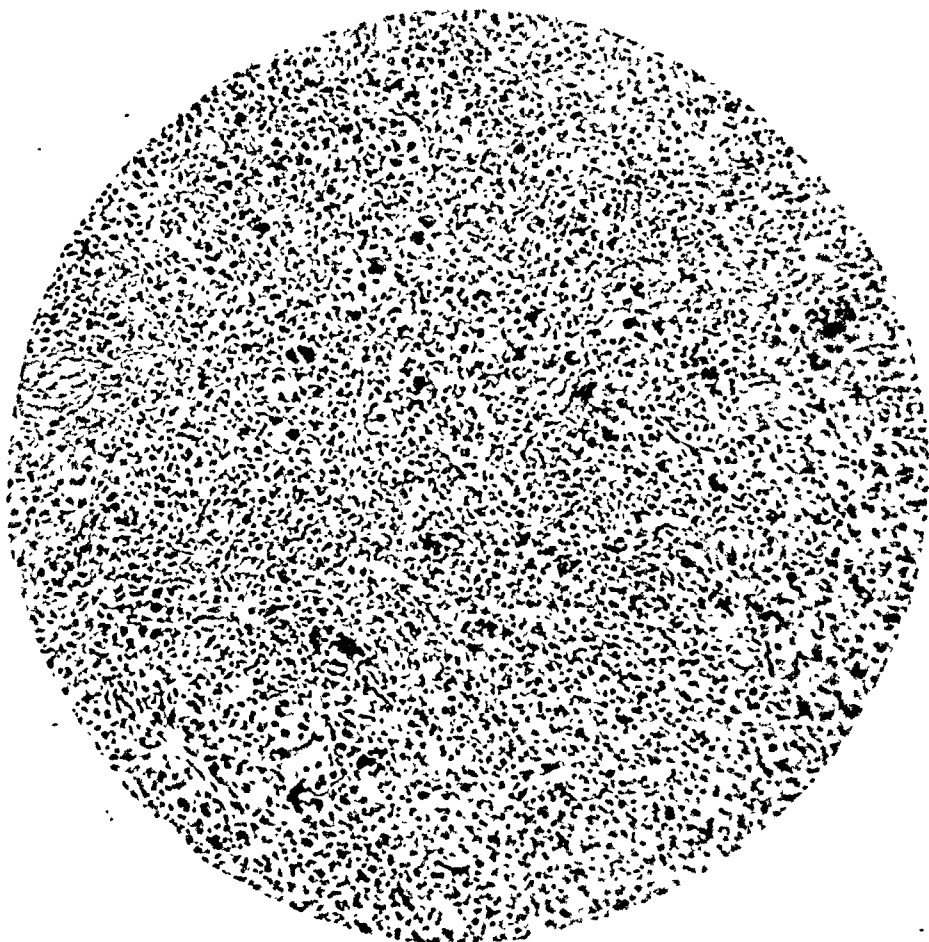


FIG. 3. Photomicrograph of spleen showing fibrosis and numerous Reed-Sternberg cells. H & E  $\times 75$ .

**Kidneys:** The kidneys were normal in size but the external surfaces were granular. The capsules could be stripped with ease. Both kidneys presented a normal appearance on section.

**Spleen (figure 1):** The spleen weighed 820 gm. and measured 19 by 14 by 5 cm. It was firm and meaty in consistency. The external surface was mottled pink red and purple and contained a firm gray white infarct measuring 3.5 by 1.5 cm. near the lower pole. On section the spleen was mottled pink and red. The Malpighian follicles were not seen and the fibrous markings were increased. The pulp could be scraped with difficulty. The splenic vein and artery showed nothing of note.



**Lymph Nodes:** A careful examination of all the lymph nodes failed to reveal any change in consistency or enlargement of any.

**Bone Marrow:** Sections from the vertebrae showed the marrow to be grossly abundant and red.

*Histologic Examination:* **Heart:** The heart showed a moderate amount of fibrosis.

**Lungs:** The right lung was completely involved by a lobar pneumonia in the gray hepatization stage. The left lung showed compensatory emphysema.

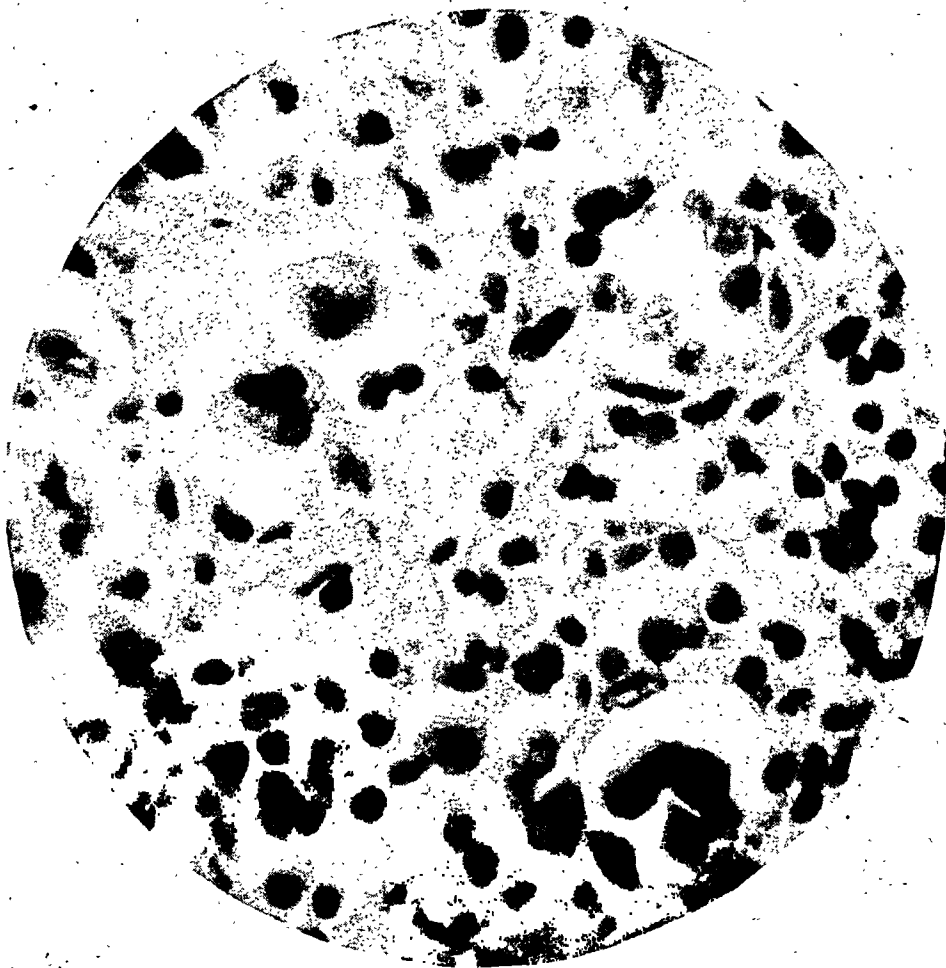


FIG. 4. Photomicrograph of spleen showing details. H & E  $\times 320$ .

**Liver (figure 2):** The liver cells were arranged into cords and cords into lobules in an orderly fashion. The sinusoids were all dilated and engorged with blood. Many of them also contained large mononuclear and multinucleated giant cells of the Reed-Sternberg type. The liver cell cords were compressed and many of the liver cells were vacuolated. Almost all contained brown pigment granules.

**Pancreas and Adrenal Glands:** These showed nothing of note.

**Kidneys:** Preparations from the kidneys showed benign nephrosclerosis in a moderately advanced stage.

**Spleen (figures 3 and 4):** The capsule was thickened and the Malpighian corpuscles obliterated. There was an increase in fibrous tissue throughout the spleen

and an infiltration with round mononuclear cells and giant cells some of which were multinucleated while others contained one or two deeply staining nuclei. These latter cells were of the Reed-Sternberg type. One preparation contained a large area of necrotic pale staining splenic tissue. No eosinophiles were seen in the spleen.

Bone (figure 5): Preparations from the vertebrae showed fibrosis of the marrow and infiltration with large cells of the Reed-Sternberg type. A marked increase in eosinophilic cells was also present.

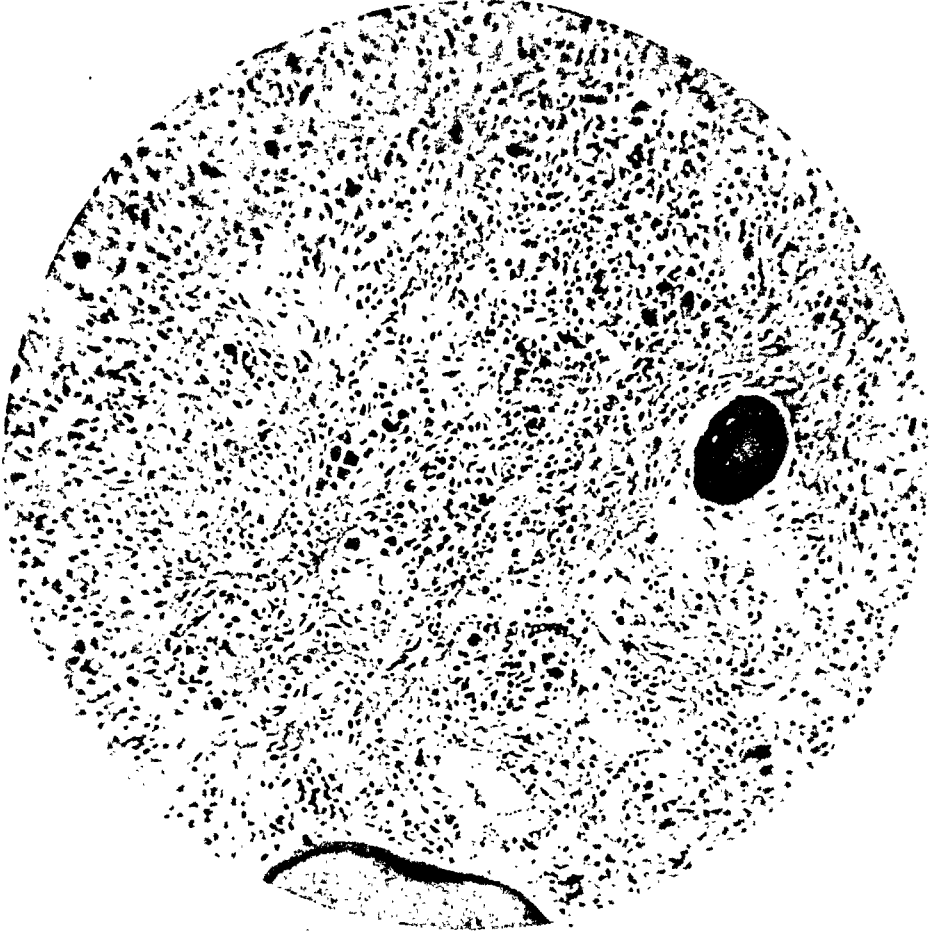


FIG. 5. Photomicrograph of vertebra showing fibrosis, Reed-Sternberg cells, and eosinophils. The eosinophils are not clear in this black and white picture. H & E  $\times 75$ .

*Anatomic Diagnosis:* Hodgkin's disease in spleen and bone marrow; pneumonia, diffuse, right; emphysema in lung, left; congestion of viscera; myofibrosis cordis; fatty changes in liver; nephrosclerosis; fibrous pleural adhesions; cholecystitis; cholelithiasis, chronic.

#### DISCUSSION

It is impossible completely to rule out lymph node involvement in this case as well as in previous cases. To do so would necessitate serial sections of all the lymph nodes in the body, an obviously impossible task. Short of that, an ex-

ceedingly careful search was made of every available lymph node, superficial or deep, but none showed any alteration in size or consistency. It is felt, therefore, that this is a true case of primary splenic Hodgkin's disease.

Hodgkin's disease should no longer be regarded as "a disease of lymph nodes," as every medical author describes it, but rather as a disease of the reticulo-endothelial system. The involvement is at first local, and then generalized. Accordingly, the lesions may be found wherever this system exists; in the lymph nodes, spleen, liver or bone marrow.

Gebauer<sup>9</sup> in making the clinical diagnosis of primary splenic Hodgkin's disease stressed the following criteria: (1) Enlarged spleen and liver. (2) Pel-Ebstein fever. (3) Weight loss. (4) Blood picture. The latter comprises severe anemia, leukopenia, thrombocytopenia and lymphocytosis. The anemia is so severe that in the four previous cases proved at autopsy,<sup>6, 7, 8, 9</sup> and in ours, the presenting symptoms were weakness, dyspnea and ankle edema and the hemoglobin determinations in all cases were between 25 to 35 per cent. Furthermore, this anemia responds poorly, if at all, to blood transfusions and hematinics. In the generalized form of Hodgkin's disease the anemia seldom approaches this severity. The generalized form is frequently characterized by leukocytosis and eosinophilia and depression of the platelets is not seen. Marked leukopenia and lymphocytosis is the rule in the primary splenic form, and eosinophilia has not yet been described in the peripheral blood smears. There is distinct thrombocytopenia. All these changes are doubtless due to bone marrow involvement.

In the differential diagnosis Gebauer lists leukemia, sepsis, miliary tuberculosis, typhus fever, brucellosis, malaria and hemolytic icterus. Since these are readily ruled out, a diagnosis of primary splenic Hodgkin's disease can be established by exclusion. An aid suggested by Velasco Montes<sup>10</sup> is splenic puncture, which, according to him, is a simple, harmless procedure. The presence of Reed-Sternberg cells and eosinophiles establishes the diagnosis.

### CONCLUSIONS

Hodgkin's disease is a disease of the reticuloendothelial system and not of the lymphatic apparatus alone. Primary splenic Hodgkin's disease is a distinct entity and can be clinically diagnosed once its existence is generally realized.

### BIBLIOGRAPHY

1. HODGKIN, TH.: *Trans. Med. Chir. Soc., London*, 1832, xvii, 68.
2. REED, D. M.: Pathological changes in Hodgkin's disease with especial reference to tuberculosis, *Johns Hopkins Hosp. Rep.*, 1902, x, 133.
3. SYMMERS, D.: Certain unusual lesions of the lymphatic apparatus, *Arch. Int. Med.*, 1909, iv, 218.
4. WADE, A. W.: Primary Hodgkin's disease of spleen, *Jr. Med. Res.*, 1913, xxix, 209.
5. DOWD, C. N.: Splenectomy for the splenic form of Hodgkin's disease, *Ann. Surg.*, 1917, lxxv, 785.
6. KRUMBHAAR, E. B.: Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes, *Am. Jr. Med. Sci.*, 1931, clxxxii, 764.
7. SEARS and BLACK: Hodgkin's disease without lymphadenopathy, *Colorado Med.*, 1932, xxix, 208.
8. BORDONI-POSSI, RURIEL, P., and ARDAO, HECTOR: Malignant lymphogranuloma of the spleen, *Arch. urug. de med., cir. y especialid.*, 1935, vii, 33.

9. GEBAUER: Acute isolated lymphogranulomatosis of spleen, *Deutsch. Arch. f. klin. Med.*, 1939, clxxxv, 338.
10. VELASCO MONTES, F.: Puncture of spleen as diagnostic method in aleukemic lymphadenosis and in differential diagnosis of various splenomegalies, especially of pure lymphogranulomatosis, *Med. Klin.*, 1939, xxxv, 249.

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## CARCINOMA OF THE PANCREAS WITH PULMONARY LYMPHATIC CARCINOMATOSIS SIMULATING BRONCHIAL ÁSTHMA: CASE REPORT\*

By CHARLES F. SWEIGERT, Lt. Col., M.C., EDWARD F. McLAUGHLIN, Lt. Col., M.C., and ERLE M. HEATH, Capt., M.C., *Lincoln, Nebraska*

SEVERAL reports in the recent literature<sup>1, 2, 3</sup> have stressed the appearance of asthmatic symptoms as a manifestation of pulmonary metastases from abdominal neoplasms. Mendeloff<sup>1</sup> presented two cases with severe asthmatic dyspnea as the sole manifestation of generalized endolymphatic carcinomatosis. A case of carcinoma of the pancreas with metastasis to the lungs which had been clinically treated as bronchial asthma was described in the case records of the Massachusetts General Hospital.<sup>2</sup> Denenholz and Cheney<sup>4</sup> mentioned a case under observation for coccidioidomycosis or tuberculosis in which, although asthma was not reported, the dominant clinical features were respiratory. Wu<sup>3</sup> studied a series of 49 cases of "lymphangitis carcinomatosa" selected from the literature. It is felt that the following case report of carcinoma of the pancreas with lymphatic metastasis to the lungs will serve further to emphasize the association of respiratory symptoms with cancer arising elsewhere in the body.

### CASE REPORT

A 22 year old white male was admitted to the Regional Hospital on April 24, 1945 complaining of pain in the right upper quadrant of the abdomen of six weeks' duration, paroxysmal dry cough of two months' duration, and a loss of 15 to 20 pounds over a two months' period.

*History:* The past medical, personal and family history were essentially negative. Prior to induction into the Army he had been a student. He had had no foreign service and no previous serious illness.

The patient felt well until about March 15, 1945, at which time he noted the gradual onset of dull, burning epigastric pain. This consisted of a dull sensation of soreness, more marked about one to one and one-half hours after eating. It was aggravated by sudden jarring movement and relieved by doubling up into a jack-knife position but not by taking food. He was hospitalized originally at a satellite station hospital on March 28, 1945. At that time he had some tenderness in the epigastrium but no palpable mass. A flat plate of the abdomen showed no gas beneath the diaphragm and a barium series showed a wide duodenal loop (figure 1) but was otherwise negative. Laboratory findings showed a normal red and white blood count and urinalysis. Stool examination was negative for blood on two occasions; icteric index was 5 on both April 3 and April 19, 1945. Sedimentation rate was 19 mm. per hour. Kahn test was negative. Serum amylase was reported as 800 mg. of re-

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ducing sugar produced per 100 c.c. of blood, on April 4; 533 mg. on April 5; and 320 mg. on April 17, 1945. On a bland, low-residue diet the epigastric pain subsided about April 10, 1945. About April 14, however, he developed a pain in the right

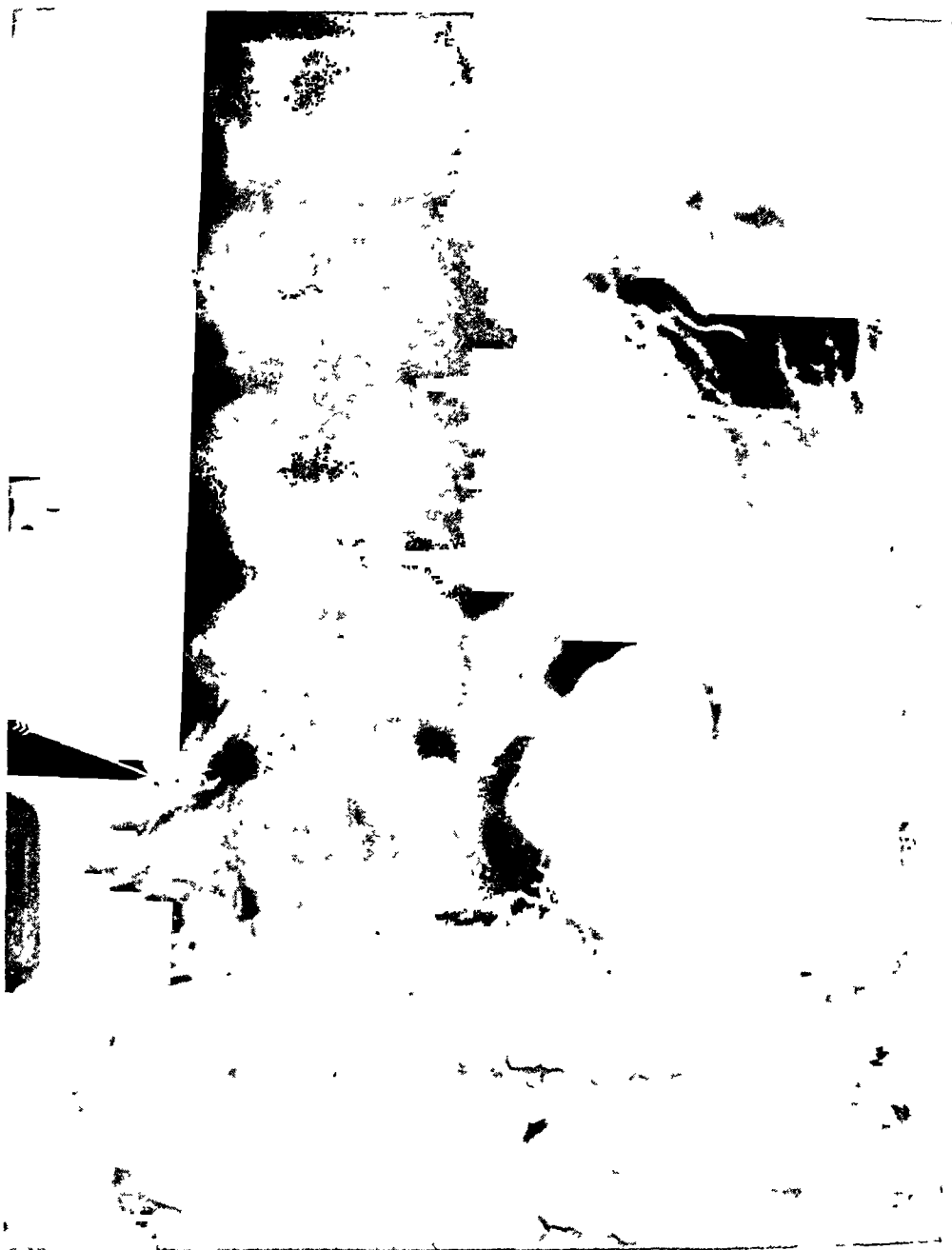


FIG. 1. Showing widening of duodenal loop.

upper quadrant of the abdomen. This was rather steady and deep with no radiation and was relieved only by the jackknife position or by codeine. It was quite severe in intensity and unrelated to food. No definite diagnosis was made at this time, and the patient was transferred to Regional Hospital, Lincoln, Nebraska, April 24, 1945, for further observation

*Physical Examination:* At the time of admission the patient had a slight yellowish tint to the sclera and skin. He was thin and apparently dehydrated. Examination of the lungs revealed a few fine and sibilant râles at both bases. The cardiovascular system was normal. The abdomen was flat and fairly rigid throughout the entire

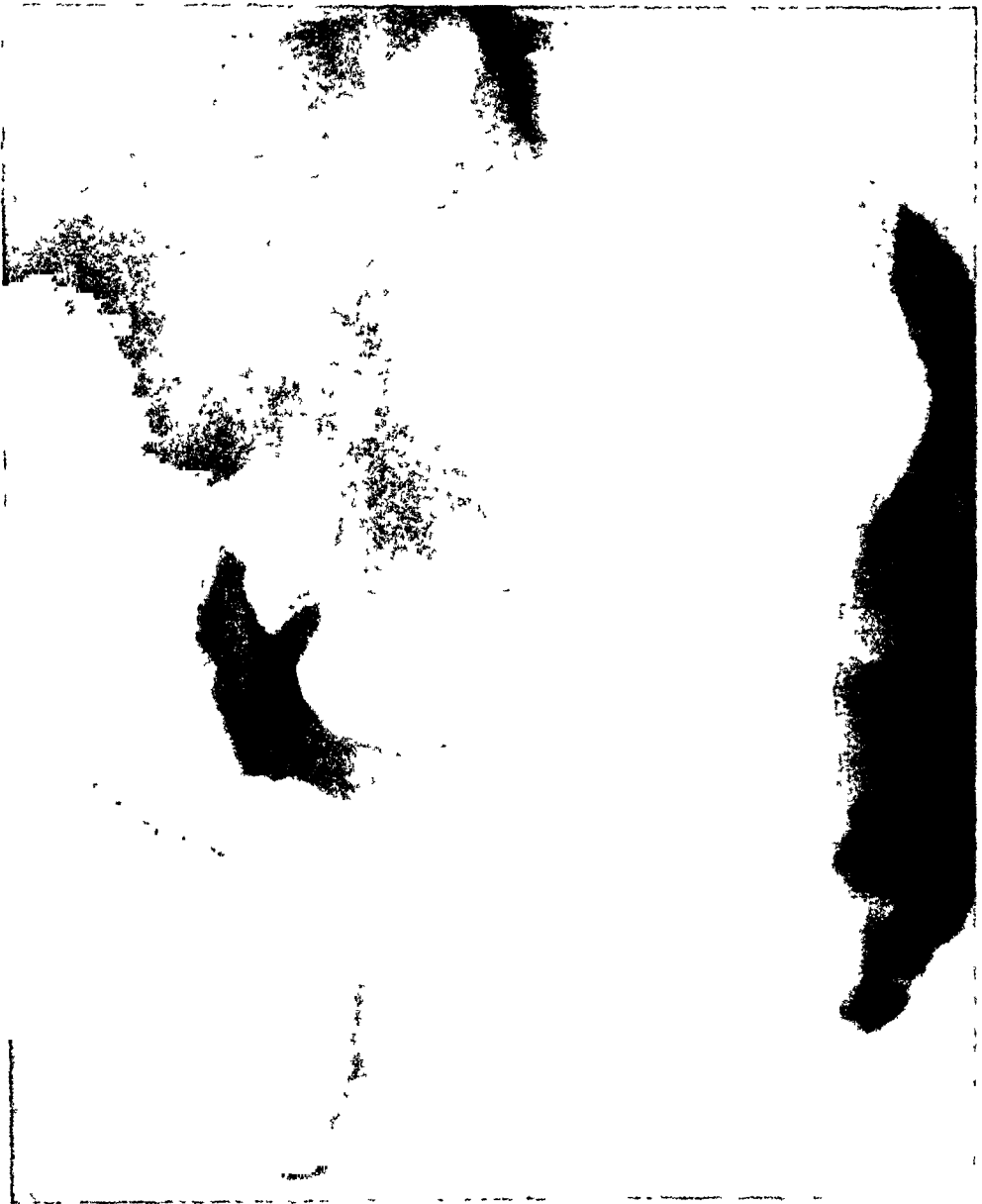


FIG. 2. Showing apparent defect of lesser curvature of stomach.

upper portion. There was definite localized tenderness in the right upper quadrant about 4 to 6 cm. to the right of the midline. There were no definite palpable masses at this time, but there was a sense of resistance in the right upper quadrant.

*Course:* After admission his pain remained unchanged and required codeine and aspirin for relief. He was observed frequently to sit in bed in a jackknife position so that his knees were doubled up onto his abdomen. He stated that this gave him

some relief from the pain. Icterus became progressively more marked and by April 27 the patient was clinically jaundiced. On April 28, for the first time, a firm, irregular, tender mass not well outlined, was palpable in the epigastrium. At this time asthmatic wheezes were heard diffusely over the chest, especially on the right side. Laboratory findings at this time were as follows: Urinalysis was negative; urobilinogen urine test was positive in dilution 1:2, on April 30. Serum amylase was 180 Somogyi units on April 20. The icteric index was 29, and the van den Bergh a direct positive on April 26. The white blood count was 6,300, and red blood count 5,120,000. Sedimentation rate was 30 mm. on April 26, and 46 mm. on April 30. Blood sugar was 125 mg. per cent. Blood chlorides were 439 mg. per cent on April 30. Kahn test was negative. Gastrointestinal series revealed a constant defect of the lesser curvature of the stomach which was visible when the patient was turned about 70° in the oblique position (figure 2). There appeared to be some widening of the duodenal loop (figure 1).

Chest roentgenogram on April 30, 1945 (figure 3) showed a dissemination throughout both lung fields of a definite infiltrating increased density. This was a peribronchial infiltration more marked at the hilar regions but also extending along the cardiac borders and outward toward the periphery of the lungs. No portion of the lungs was spared.

*Preoperative Impression:* The preoperative impression was that this patient had an abdominal cancer with lymphatic metastasis to the lungs. The most probable site of tumor was thought to be the pancreas although an intrinsic neoplasm of the digestive tract could not be excluded. An exploratory laparotomy was performed May 5, 1945.

*Operative Findings:* The abdomen was opened through a high right rectus incision and immediately beneath the anterior parietes the pyloric end of the stomach and duodenum were encountered. Beneath them and displacing them forward was a nodular firm mass about 8 cm. in diameter. It extended and tapered off to the left, apparently replacing all normal pancreatic tissue. Enlarged hard lymph nodes were palpated in the gastrohepatic omentum. One of these, together with a section from the tumor mass, was removed for examination. The common duct was distended and the gall-bladder collapsed. This was a somewhat paradoxical finding, explained when the cystic duct was exposed and found to be hard and contracted due to infiltration by a neoplastic growth. The liver was normal in size and not grossly involved. The stomach showed no pathological changes. The spleen was slightly enlarged but otherwise normal. Hard nodes were present in the gastrocolic omentum. The remainder of the abdominal contents was normal. The abdomen contained a moderate amount of bile-tinged free fluid. The common duct was opened and probed and a complete obstruction found near its lower end. A T-tube was inserted into the duct, a cigarette drain placed in the area, and the abdominal wall closed about them.

*Postoperative Course:* Postoperatively the patient's jaundice was relieved by drainage through the choledochostomy. Postoperative management otherwise consisted of relief of pain and the institution of a bile replacement program. The measured drainage of the bile stayed close to 500 c.c. per day. This bile was desiccated and administered in capsule form (7 to 16 capsules daily of approximately 0.65 gram each). This program resulted in return of the stools to normal color and maintenance of an average prothrombin time of 90 per cent of normal without artificial aid. By May 17, 1945, a definite increase of frequency and severity of the paroxysms of cough was noted. The patient also had a progressive increase in pain and by May 30 he had a constant dull pain in the epigastrium, always partially relieved by the jackknife position. The patient's postoperative course was characterized by progressive failure, weakness, pain, increasing respiratory distress and emaciation. At

this time constant diffuse sibilant râles and asthmatic wheezes were heard throughout both lung fields, presenting the clinical picture of severe, intractable bronchial asthma. The patient had frequent severe paroxysms of cough and marked dyspnea and wheezing, plainly audible at a distance. He failed rapidly and died June 14.



FIG. 3. Showing disseminated infiltrating type of density in the lungs.

1945. The total duration of the illness from the onset of the first symptoms was two months.

*Autopsy Findings:* At necropsy, marked wasting and jaundice were evident. The abdominal viscera appeared to be normally disposed. However, the pyloric end of the stomach and the duodenal loop were displaced forward by an underlying mass. The lymph nodes at the root of the mesentery and those surrounding the colon were



enlarged and firm. The mass, about 8 by 5 by 5 cm. in size, was located behind the stomach and duodenal loop. A greater portion of the mass lay in the region of the pancreas and along the first portion of the duodenum at the junction of the common bile and pancreatic ducts. No normal pancreatic tissue was found; rather, the pancreas was replaced by a grayish-white homogeneous mass which cut with considerable resistance. The gall-bladder was completely collapsed and slightly thickened. The cystic duct was completely obstructed approximately 1.5 cm. from its junction with the common duct. Distal to the T-tube the common duct was completely occluded and a probe could not be passed into the duodenum. The liver was studded with grayish-white nodules 0.5 to 2.5 cm. in diameter. On the inferior surface of the liver there was a grayish-white extension from the tumor mass. On the external surface of the lungs there were grayish-white linear seedings of discrete, hard, BB-shot nodules. The tracheal, bronchial, and bronchopulmonary nodes were enlarged and firm. The left lower lobe bronchus was almost completely occluded at several points along its course by the enlarged colorless nodes. The lungs cut with a gritty hard sensation. All lung lobes, except the right lower lobe, were consolidated and an abscess cavity 4.5 cm. in diameter was found in the left lower lobe.

*Microscopic Report:* Microscopic sections of the pancreas consisted almost completely of infiltrating adenocarcinoma. However, some areas were seen to contain an admixture of tumor cells and a few surviving pancreatic acini. All sections of the lungs showed a profuse proliferation of tumor cells with partial obliteration of the normal lung structure. The alveolar spaces were partially lined by infiltrating tumor cells and free tumor cells were seen in many spaces. In the liver there was extensive destruction of the normal hepatic architecture by infiltrating adenocarcinoma. In addition, metastases were noted in the hilar lymph nodes, common bile duct, adrenal glands, stomach and vertebrae. Sections from the brain, heart, gall-bladder, spleen and kidneys were free of metastasis.

*Pathological Diagnosis:* Carcinomatosis resulting from dissemination of pancreatic adenocarcinoma to the lungs, bronchial lymph nodes, liver, adrenals and vertebrae.

## DISCUSSION

This case was unusual in several respects. First, it presented a difficult differential diagnostic problem. Secondly, it illustrates the occurrence of bronchial asthma secondary to pulmonary lymphatic metastasis and the association of the latter with primary abdominal cancer. In addition, the age of the patient, 22 years, is unusual, and the duration of the entire illness (two months) was strikingly brief.

The differential diagnosis involved consideration of several possibilities. The onset with rather marked burning epigastric pain and upper abdominal tenderness along with the defect of the lesser curvature seen on roentgenogram (figure 2) suggested the possibility of a gastric ulcer. The increased serum amylase maintained over a period of several weeks, though not typical of an acute pancreatitis, suggested pancreatic involvement. The age of the patient, the cough, râles and wheezes, and the chest roentgenogram (figure 3) suggested the possibility of either tuberculosis, silicosis, sarcoid or Hodgkin's disease. The progressive development of jaundice focused attention on the biliary system. However, the marked weight loss, the palpable mass, the progressive jaundice, the wide duodenal loop demonstrated roentgenographically, and the pulmonary symptoms and signs, if assumed to be due to one disease process, could be explained only on the

basis of a neoplastic mass in the region of the upper gastrointestinal tract with metastasis to the lungs. The elevated serum amylase and the location of the mass suggested the pancreas as the most likely site of the primary growth. The preoperative diagnosis was: Intra-abdominal malignant growth, probably pancreatic, with lymphatic metastasis to the lungs.

This case differs from those described by Mendeloff<sup>1</sup> in that pulmonary symptoms were not the sole presenting complaints. However, the pulmonary symptoms and signs were sufficiently prominent to play an important rôle in the preoperative diagnosis. In Wu's<sup>5</sup> review of 30 cases of generalized lymphatic carcinomatosis of the lungs the most frequent site of primary tumor was the stomach; others were the breast, prostate, pancreas, intestines, liver, pharynx, gall-bladder, appendix, bladder and rectum. The most marked symptom of carcinomatosis of the lungs is usually progressively severe dyspnea. Paroxysmal dry cough, however, is a frequent symptom and, as in this case, may be the first respiratory symptom noted. These symptoms, when accompanied by marked weight loss, anorexia and other nonspecific manifestations of malignancy, should suggest the possibility of pulmonary carcinomatosis. Roentgenograms are suggestive of this, although not conclusive. Similar findings may occur in silicosis, miliary tuberculosis, pulmonary fibrosis, coccidioidomycosis and the lymphomata.

The method of spread to the lungs is generally thought to be a direct extension along the lymphatics. Greenspan<sup>6</sup> described the effect of carcinomatous lymphangitis on the production of obliterative endarteritis with resultant right heart failure. Schattenberg and Ryan<sup>3</sup> reported some observations which support the possibility that some tumor cells may gain entrance to the venous circulation through the thoracic duct. The postmortem pathology of these patients has been adequately described by Schattenberg and Ryan.<sup>3</sup>

As to the surgical care of this patient, it would have been desirable, in view of such apparent widespread malignancy, to have avoided laparotomy. However, because of the increasing and distressing jaundice and because the exact nature of the intra-abdominal lesion was not definitely established, it was felt that laparotomy was indicated. Because of the extensive neoplastic involvement, definitive surgery was out of the question. Cholecystoenterostomy would have been desirable but because the cystic duct was involved in the malignant process and completely obstructed, this could not be done. External biliary drainage, using a T-tube in the common duct was the only practicable procedure. When cancer is so rapidly spreading and overwhelming, surgery, of course, has little to offer except to assist in establishing the diagnosis and to provide palliative measures for the relief and comfort of the patient. The extent of the process in this patient was evidenced preoperatively more by the chest findings and the roentgenograms than by the local abdominal findings.

### SUMMARY

A case of carcinoma of the pancreas with lymphatic metastasis to the lungs is presented along with a brief discussion of the symptomatology, differential diagnosis, and pathogenesis. The clinical features of this case emphasize the need of considering carcinomatous metastases as a cause of asthmatic symptoms and diffuse pulmonary infiltrations.

## BIBLIOGRAPHY

1. MENDELOFF, A. I.: Severe asthmatic dyspnea as the sole presenting symptom of generalized endolymphatic carcinomatosis, *Ann. Int. Med.*, 1945, xxvii, 386.
2. Case No. 30032, *New England Jr. Med.*, 1944, ccxxx, 87.
3. SCHATTENBERG, H. J., and RYAN, J. F.: Lymphangitic carcinomatosis of the lungs; case report with autopsy findings, *Ann. Int. Med.*, 1941, xiv, 1710.
4. DENENHOLZ, E. J., and CHENEY, G.: Diagnosis and treatment of chronic coccidioidomycosis, *Arch. Int. Med.*, 1944, lxxiv, 311.
5. WU, T. T.: Generalized lymphatic carcinosis ("lymphangitis carcinomatosa") of the lungs, *Jr. Path. and Bact.*, 1936, xliii, 61.
6. GREENSPAN, E. O.: Carcinomatous endarteritis of pulmonary vessels resulting in failure of the right ventricle, *Arch. Int. Med.*, 1934, liv, 61.

## COMPLETE TRANSPOSITION OF THE ARTERIAL TRUNKS WITH CLOSED INTERVENTRICULAR SEPTUM \*

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SINCE Abbott's<sup>1</sup> clinical classification of congenital anomalies of the heart, much interest has been manifested in the diagnosis and specific anatomical defects of these conditions. On a clinical basis she has classified these anomalies into three great groups, as follows: (1) Acyanotic group—cases without abnormal communication between the two sides of the heart, (2) cyanosis tardive group—cases of arterial-venous shunt with transient or terminal reversal of flow, and (3) cyanotic group—cases of venous-arterial shunt. It is the latter, the cyanotic group, into which the anomaly of transposition of the great vessels falls. Since our discussion will be concerned mainly with this anomaly, space will not permit enumeration or description of the other anomalies of this group.

Transposition of the arterial trunks refers to an abnormal relationship in the origin of the aorta and pulmonary artery. The degree of transposition depends primarily upon the stage at which normal embryonal development is interrupted, as is basically true of all congenital heart anomalies. Abbott<sup>1</sup> in an analysis of 1,000 cases classifies this anomaly as follows: (1) Dextro-position of the aorta, in which this vessel arises from a position to the right of the normal, viz., from the left ventricle (with intact septum), from both ventricles (overriding a septal defect), or from the right ventricle with a double conus, (2) partial transposition, in which both arterial trunks arise from the same ventricle, (3) corrected transposition, in which the aorta and pulmonary artery are in abnormal relation to each other, yet arise from their proper ventricles, and (4) complete transposition (also called crossed transposition), in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle.

Of 1,000 cases of congenital heart disease analyzed by Abbott<sup>1</sup> complete transposition of the great arterial trunks was the primary defect in 49, of which 32 had closed ventricular septa and 17 had ventricular septal defects.

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Complete transposition of the arterial trunks is always associated with another anomaly, permitting communication between the right and left sides of the heart, for otherwise blood of the systemic circulation could not become oxygenated. There are three anatomical openings which permit passage of blood between the two sides of the heart and occur singly or in combination. These openings are: interauricular septal defect, interventricular septal defect, and communications between the aorta and pulmonary artery (usually patent ductus arteriosus). Kato<sup>2</sup> reviewed the cases of complete transposition reported in the literature prior to 1929 and discovered 92 such cases, to which he added five of his own. This series of 97 cases we have reviewed in table 1, which reveals the relative frequency of the various combinations of anatomical openings between the two sides of the heart occurring in combination with complete transposition of the great vessels.

TABLE I

Analysis of 97 Cases of Transposition of the Arterial Trunks Reviewed by Kato,<sup>2</sup> to Show the Relative Frequency of Associated Anomalies

Transposition of the Arterial Trunks	
1. Closed ventricular septum, occurring . . . . .	50
a. alone . . . . .	0
b. with patent foramen ovale . . . . .	12
c. with patent ductus arteriosus . . . . .	9
d. with patent foramen ovale and ductus arteriosus . . . . .	27
e. with pulmonary artery arising from aorta . . . . .	1
f. with pulmonary artery arising from aorta with patent ductus arteriosus . . . . .	1
2. Open ventricular septum, occurring . . . . .	45
a. alone . . . . .	12
b. with patent foramen ovale . . . . .	19
c. with patent ductus arteriosus . . . . .	5
d. with patent foramen ovale and ductus arteriosus . . . . .	9
3. Data insufficient . . . . .	2
Total . . . . .	97

In 86 cases of this anomaly reviewed by Kato<sup>2</sup> in which the age was stated; the maximum age at which death occurred was 56 years. The average length of life was 2.3 years; however, since only four patients lived longer than four years (56, 21, 21, and 19 years), a more representative average of 7.8 months is obtained by omitting these four cases.

The symptomatology is variable. There may be observed no symptoms, especially in those patients who succumb after a few days or weeks of life. On the other hand, any one or more of the symptoms occurring in congenital heart disease may be encountered, especially those of the respiratory, cerebral, and gastrointestinal systems. Of these, the most frequently encountered are dyspnea, convulsions, anorexia, and regurgitation of food. Of the physical findings, cyanosis is by far the most common and is almost invariably present except in early infancy when it may be absent. Cyanosis is usually aggravated by exertion, such as occurs with crying or feeding. Clubbing of the digits is frequently present in patients who survive for longer than a few weeks. The heart is usually enlarged, especially the right ventricle, as may be shown by roentgen examination and by an abnormal right axis deviation of the electrocardiogram. Murmurs and thrills are not constant findings, and when present are dependent upon an accompanying

septal defect or patent ductus arteriosus. Of 49 cases of complete transposition analyzed by Abbott,<sup>1</sup> 19 presented murmurs; of the 32 cases with intact ventricular septa systolic murmurs were present in eight, and of the 17 cases with inter-ventricular septal defects systolic murmurs were found in 10 and a double murmur in one.

The diagnosis of complete transposition of the arterial trunks is rarely made except at autopsy. Taussig<sup>3</sup> in 1938 called attention to four ante-mortem findings the combination of which she considered to be characteristic of this condition: (1) Persistent cyanosis, (2) cardiac enlargement, especially of the right ventricle, (3) narrow aortic shadows in the antero-posterior roentgenogram, and (4) an increase in the width of the roentgenographic shadow of the great vessels in the anterior oblique position.

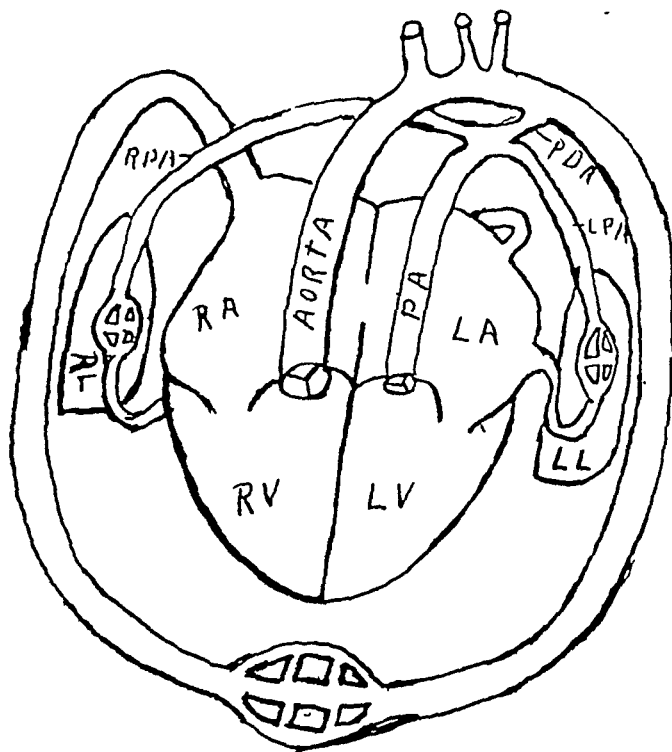


FIG. 1. Schematic drawing representing complete transposition of the arterial trunks with patent foramen ovale and ductus arteriosus. R.A., right auricle; L.A., left auricle; R.V., right ventricle; L.V., left ventricle; P.A., pulmonary artery; R.P.A., right pulmonary artery; L.P.A., left pulmonary artery; P.D.A., patent ductus arteriosus; R.L., right lung; L.L., left lung. (Reproduction by U. S. Army Signal Corps.)

#### CASE REPORT

A white male infant, the second of uniovular twins, was born May 15, 1945 at 7:44 a.m. The first-born twin, also a male, was delivered at 7:35 a.m. on the same date. Both were full term and were delivered by version and breech extraction without difficulty. The duration of labor was 24 hours. The common placenta and the cords were of normal appearance.

The first-born twin weighed six pounds and 13 ounces (3.1 kg.) at birth and was never noted to be cyanotic. Examination prior to discharge from the hospital on May 28, 1945 revealed no abnormalities. During routine examination at age four

weeks a loud, blowing, systolic murmur at the base of the heart was heard. An electrocardiogram made that date was normal. At age two months the infant was seen by the parents to suddenly become cyanotic and die within two hours. Just before death the infant was examined by the resident pediatrician of a nearby hospital, who



FIG. 2 Roentgen-ray made at age one day showing the size of the heart. (Reproduction by U. S. Army Signal Corps.)

expressed the opinion that death was due to acute cardiac failure. Permission for autopsy was refused.

Both parents were healthy and blood Kahn reactions for syphilis were reported as negative. There was no history suggestive of congenital heart disease in the family. This was the mother's first pregnancy.

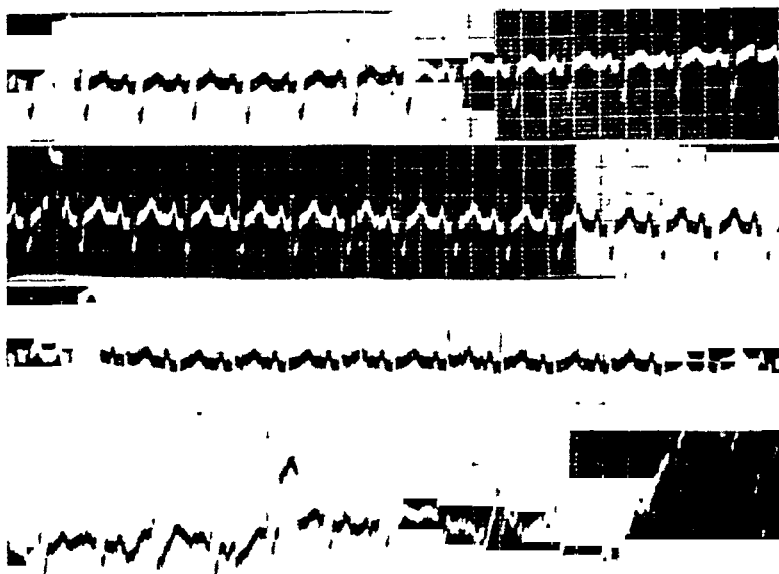
The last-born twin, the subject of this report, weighed six pounds and five ounces (287 kg.) at birth and was noted to be moderately cyanotic, the color varying in

intensity with exertion or crying. There was noted no stridor, dyspnea, or convulsive seizures. The infant was bottle-fed and developed normally except for varying degrees of cyanosis. On June 1 examination revealed a fairly well-nourished, moderately cyanotic infant. Examination of the heart revealed no enlargement, thrills, abnormal sounds or accentuations, murmurs, or arrhythmias. The clinical chart indi-



FIG. 3. Roentgen-ray made at age one month showing contour and enlargement of the heart.  
(Reproduction by U. S. Army Signal Corps.)

cated that the infant continued to gain weight and showed no significant change until June 12, when a more severe attack of cyanosis prompted the administration of oxygen by B-L-B mask. At 4:15 p.m. on June 22 respirations became slow and weak, the lungs were normal, and the lower border of the liver was palpated 5 cm. below the right costal margin. Coramine, oxygen, and artificial respiration were administered before death, which occurred at 4:55 p.m. on June 22, 1945.



4. Electrocardiogram made at age two weeks showing right axis deviation. (Reproduction by U. S. Army Signal Corps.)



5. Photograph of the heart: Right ventricle opened, with probe in aorta arising from right ventricle. (Photo by U. S. Army Signal Corps.)



*Laboratory and Special Examinations:* On May 20 the blood showed hemoglobin 18 gm. (Sahli), red blood cells 5,800,000, white blood cells 6,100, with neutrophils 40 per cent, lymphocytes 55 per cent, and eosinophiles 5 per cent.

Roentgen examinations of the chest showed normal lung shadows and progressive enlargement of the heart, which presented a globular appearance. The cardio-thoracic ratio showed the following changes on successive films: 56 per cent on May 16 (figure 2), 59.2 per cent on May 28, and 61 per cent on June 16 (figure 3).



FIG. 6 Photograph of the heart: Left ventricle and auricle opened, with probe in patent foramen ovale. (Photo by U. S. Army Signal Corps.)

An electrocardiogram (figure 4) made on June 1, 1945 revealed the following: The tracing showed a definite right axis deviation, the QRS complexes in Leads I and II being of the N type, with  $S_1$  slightly greater than  $R_1$ , while  $S_2$  and  $R_2$  were equidistant. The main deflection of  $QRS_3$  was up. There was regular sinus rhythm; the rate was 140 per minute. The P waves were of normal duration, size and contour. The S-T-T combinations showed no abnormalities. Interpretation: Sinus tachycardia and right ventricular preponderance, compatible with the clinical diagnosis of congenital heart disease

*Autopsy Examination:* General: The body was that of a well developed, well nourished, white male infant appearing about the stated age of five weeks. The head, neck, thorax, abdomen, and extremities were normal. The skin showed a marked degree of cyanosis, and postmortem lividity and rigor mortis were fairly well developed. The infant weighed 7 pounds and 5 ounces (3.64 kg.). Primary incision: An incision was made from the suprasternal to the xiphoid notches, and the autopsy was limited to the thorax. The rib cage was lifted off in the usual manner and the pleura inspected. No adhesions were found. The left pleural cavity contained 50 c.c. of yellowish serous fluid. Heart and lungs: The heart and lungs were removed in mass: Both lungs were edematous and on cut surface oozed frothy fluid. No areas of consolidation, hemorrhage, or infarction were found, although in the dependent portions there was some atelectasis. The heart was enlarged. The pericardial sac appeared normal, being free of fluid and adhesions. The overall measurements of the heart were 6 cm. by 5 cm. by 3 cm. The wall of the left ventricle measured 5 mm. in thickness, and that of the right measured 4 mm. The coronary system appeared normal. The aorta arose from an enlarged right ventricle (figure 4) and communicated with the pulmonary artery through a very wide patent ductus arteriosus. The pulmonary artery arose from the left ventricle and branched into both lungs. Both vessels were guarded by a three-cusp semilunar valve. The right ventricle appeared to be markedly enlarged and the wall thickened. The left ventricle was of normal size and the chamber was smaller than the right. The auricles and the atrioventricular valves appeared normal. The foramen ovale was fully patent (figure 5) and measured about 3 mm. in diameter. The interventricular septum was intact.

*Histological Examination.* Lungs: Sections of the lungs showed scattered areas in which the alveoli had not expanded. In other areas where the lung was fully expanded the septal capillaries were markedly engorged. There were numerous hemosiderin-bearing macrophages among the cells lining the alveolar sacs and within the septa. Heart: Microscopic sections of the heart showed normal epicardium with the usual covering of mesothelial cells and a myocardium composed of the normal branching syncytium of striated muscle. The endocardium appeared normal. Cause of death: Acute congestive heart failure, due to congenital cardiac disease, with transposition of the aorta and pulmonary artery, patent ductus arteriosus and patent foramen ovale.

#### COMMENT

This case represents an instance of complete transposition of the arterial trunks with closed intraventricular septum, patent foramen ovale and patent ductus arteriosus. The only significant ante-mortem findings were persistent cyanosis, progressive enlargement of the heart and marked right axis deviation of the electrocardiogram. A clinical diagnosis of congenital heart disease of the cyanotic group was made, but the exact anatomical defects were not determined until autopsy.

At autopsy considerable interest was manifested by the staff in the probable course taken by the circulation in this condition (figure 1). In 1850 a case identically similar to ours was described by Johnson,<sup>4</sup> who proposed that the direction of blood flow occurs as follows: Venous blood enters the right auricle, a greater portion of which passes into the right ventricle to be expelled into the aorta and the systemic circulation. However, this being unoxygenated blood, in order to maintain life for longer than a few minutes, a certain amount of blood must reach the lungs for aeration and does so by passage from right to left auricle through the patent foramen ovale, while at the same time a portion of aerated blood passes

from the pulmonary artery through the patent ductus arteriosus into the systemic circulation. On the other hand, there is much evidence to discredit this assumption. More recent literature supports the belief that the direction of blood-flow is from the aorta to the pulmonary artery through the patent ductus arteriosus and from the right to the left auricle through the patent foramen ovale. Most writers, including Abbott and Dawson,<sup>5</sup> who cite a similar case of Pappenheimer's, agree with the latter theory on the basis of experimental evidence that the pressure is greater in the aorta than in the pulmonary artery. Uhley<sup>6</sup> in 1942 pointed out that the most important factor in the flow of blood from the left to the right auricle in cases of interauricular septal defect is the effect of gravity, the right auricle being situated beneath the left, and the septum lying more or less horizontally.

Whatever may be the mechanism of blood-flow which actually occurs in this arrangement of cardiac anomalies, the causes of cyanosis are clearly described by White<sup>7</sup> as being dependent upon three factors: (1) Mixture of venous and arterial blood wherein the venous blood is at least 30 per cent of the total and thus passes the threshold for cyanosis, (2) dilatation of the capillaries of the skin and mucous membrane accompanying the slowing of the peripheral blood, and (3) insufficient oxygenation of the blood in the lungs.

That an autopsy on the twin of this infant was not performed is regrettable. Inasmuch as it is likely that congenital heart disease also existed in that infant, the comparison of the possible anomalous lesion or lesions with those of its identical twin might have been of considerable interest.

### SUMMARY

1. A case of complete transposition of the arterial trunks, associated with patent foramen ovale and ductus arteriosus is presented and discussed.

2. This combination of anatomical defects is relatively rare, occurring 27 times in 97 cases of complete transposition of the arterial trunks analyzed by Kato.<sup>2</sup>

3. The theories regarding the direction of blood-flow have been presented and discussed.

### BIBLIOGRAPHY

1. ABBOTT, M. E.: Congenital cardiac diseases, Osler's Modern Medicine (McCrea), Second Edition, 1915, Lea and Febiger, Philadelphia, iv, 342-343.
2. KATO, K.: Congenital transposition of cardiac vessels—a clinical and pathological study *Am. Jr. Dis. Child.*, 1930, xxxix, 363.
3. TAUSSIG, H. B.: Complete transposition of the great vessels, *Am. Heart Jr.*, 1938, xvi, 728.
4. JOHNSON, C. P.: Cyanosis produced by transposition of the orifices of the aorta and pulmonary artery, *Am. Jr. Med. Sci.*, 1850, xx, 270.
5. ABBOTT, M. E., and DAWSON, W. T.: The clinical classification of congenital cardiac disease, with remarks upon its pathological anatomy, diagnosis and treatment, *Internat. Clin.*, 1924, iv, 156-158.
6. UHLEY, M. H.: Lutenbacher's syndrome and a new concept of the dynamics of interatrial septal defects, *Am. Heart Jr.*, 1942, xxiv, 315-328.
7. WHITE, P. D.: Heart disease, Third Edition, 1944, Macmillan Co., New York, 277-280.

## EDITORIAL

### *ACQUIRED RESISTANCE TO ANTIBIOTICS*

It has long been recognized that microörganisms may acquire a marked degree of resistance to a drug as a result of exposure to sublethal concentrations, although originally they were highly sensitive to its action. This phenomenon was first brought to general notice by Ehrlich nearly half a century ago in his studies of the action of arsenicals in spirochetal and trypanosomal infections. He applied the term drug-fast to such resistant strains.

In the more recent past many similar observations have been made with respect to the sulfonamides. Many highly susceptible species of organisms, such as the pneumococcus, the streptococcus and the gonococcus, have been found capable of acquiring such resistance, often with disconcerting rapidity. This is also true of the antibiotics penicillin and particularly streptomycin.

This resistance may be produced artificially in the laboratory by cultivating the organisms in media containing suitable concentrations of the drug. It may also develop during the course of an infection in animals or in man if the drug is given in inadequate doses or particularly if its administration is interrupted or carried out in an irregular haphazard fashion. In many cases failure to cure an infection has been shown to be associated with the development in the body of resistance to the drug by the infecting strain of the microörganism. As a rule such drug-fast strains do not differ in any other conspicuous or significant way from the strain in its original sensitive state. Its virulence is usually unimpaired. Once acquired, the resistance appears to be maintained indefinitely both in laboratory cultures and in the body.

Very little is known as to the mechanism of the antibacterial action of these drugs, although it has been assumed that they interfere with some vital metabolic activity in such a way as either to kill the cell or at least to prevent its growth and multiplication. Even less is known of the changes which render the organism resistant. It is an interesting and practically important fact, however, that acquired resistance to either the sulfonamides, penicillin or streptomycin does not affect the original susceptibility of the strain to the other drugs. The precise mechanism or site of their action is evidently different.

There are two obvious ways in which a strain of organisms might become resistant. Exposure to a sublethal concentration of the drug might bring about an adaptation as the result of a gradual progressive change in the metabolic activities of the bacterial population as a whole. This might, on the other hand, operate by killing or inhibiting the growth of the sensitive individuals and permit a few initially resistant organisms to outgrow and replace the others. The former hypothesis seems inherently improbable because of the great rapidity with which a strain may become resistant, even

within 24 hours in the case of one *H. influenzae* strain.<sup>1</sup> Recent investigations to determine this point have furnished strong direct evidence in favor of the latter alternative.

Alexander and Leidy<sup>1</sup> have reported careful studies of 14 strains of Type b *Hemophilus influenzae* derived from human infections, with respect to their sensitiveness to streptomycin. All the strains initially were sensitive to streptomycin, growth being inhibited by from one to 13 units per c.c. of medium when ordinary inocula containing from 1 million to 1700 million organisms were used. Ten patients recovered under treatment, but four did not respond to streptomycin. In three of these cases, subsequent cultures yielded strains which were resistant to this drug, growing well in media containing 1000 units per c.c.

They searched for individual organisms which were resistant to streptomycin in 10 of the initial (sensitive) strains by inoculating large quantities (142 billion to 522 billion organisms) on media containing 1000 units of streptomycin per c.c. In every case a small number of colonies of resistant organisms appeared, the incidence varying from about 1:1 billion to 1:14 billion organisms. There was no correlation between the relative number of resistant organisms found in the original cultures and the subsequent development of drug-resistance during treatment. The relative number of colonies of resistant organisms seemed to depend principally upon the size of the original bacterial population cultured. Patients with severe infections and relatively large numbers of organisms in their tissues would therefore be more likely than those with milder infections to harbor a sufficient number of drug-resistant organisms to overgrow the others and produce a resistant strain.

Miller and Bonnhoff<sup>2</sup> have reported similar studies of 18 strains of meningococci which were sensitive to streptomycin. By making large inocula on media containing streptomycin, they obtained (in 16) a few colonies of two different types of streptomycin-resistant organisms. One type closely resembled the original strain except in its resistance to streptomycin. The other differed in growing only on media containing streptomycin. It was avirulent for untreated mice, but if the mice were treated with streptomycin, it acquired virulence and the animals succumbed to the infection.

The source of the few initially resistant organisms in these cultures is a matter of interest. Alexander and Leidy<sup>3</sup> have advanced evidence to show that they possess the characteristics of bacterial mutants. Thus, there is a marked variation in the number of resistant individuals in different cultures of the same strain, depending upon how early in the growth of the culture the first resistant mutants happened to appear. The calculated rate of oc-

<sup>1</sup> ALEXANDER, H. E., and LEIDY, G.: Mode of action of streptomycin on Type b *H. influenzae*. I. Origin of resistant organisms, Jr. Exper. Med., 1947, lxxxv, 329-337.

<sup>2</sup> MILLER, C. P., and BONNHOF, M.: Development of streptomycin-resistant variants of meningococcus, Science, 1947, cv, 620.

<sup>3</sup> ALEXANDER, H. E., and LEIDY, G.: Mode of action of streptomycin on Type b *Hemophilus influenzae*. II. Nature of resistant variants, Jr. Exper. Med., 1947, lxxxv, 607-621.

currence of resistant individuals is very low, about 1/20 billion per bacterium per bacterial generation, and it was relatively constant for the different strains. The trait was transmitted unchanged through many generations. Miller and Bonnhoff concur in regarding their variants as mutations. It is, in fact, difficult to conceive of any other explanation for the origin of the strains of meningococci which required streptomycin for their growth.

Demerec<sup>4</sup> also concluded that the development of resistance to penicillin by staphylococci was the result of a mutation, since the variation in the number of resistant bacteria in samples from different cultures was much greater than in different samples from the same culture. In this case, however, he had to assume a consecutive series of mutations to explain the more gradual, steplike increase in resistance which he observed.

These observations have important practical implications. Clinical observations indicate that drug-resistance is more likely to appear in patients who are inadequately treated than in those whose treatment is efficient. Accepting the hypothesis that the resistant organisms are mutants, this observation may be explained in part by the fact that in well treated patients the multiplication of the sensitive organisms is promptly stopped and there is a smaller bacterial population from which resistant mutants might arise. There is reason to believe that the outcome depends in part upon the number of such resistant organisms present. It is probably rare that a single organism, however virulent, can initiate a progressive infection; an appreciable even if relatively small number are required. In an adequately treated patient the number of resistant organisms may be kept below that required for an adequate infecting dose, and these may then be disposed of by the natural defensive forces of the body.

The development of drug-resistant strains of organisms, however brought about, is most unfortunate, both for the individual who may succumb to the infection and from the standpoint of public health. Such resistant strains are likely to be disseminated, and as a result of natural selection they are likely gradually to replace the sensitive strains. That this may be happening is indicated by evidence which suggests that sulfonamide-fast strains of gonococci are being observed clinically with increasing frequency. The fight against infectious disease may develop into a race between man with his efforts to discover new and better antibiotics, and the microorganisms with their capacity to develop mutant forms which are resistant to the new drugs.

Another point of practical significance is the fact that organisms which become resistant to one antibiotic retain their original sensitiveness to others. This makes it rational to administer them in combination when it is feasible to do so. The few variants of *H. influenzae* which are resistant to streptomycin, e.g., retain their sensitiveness to sulfonamides, and there is a better chance of eliminating the infection completely if both drugs are administered.

P. W. C.

<sup>4</sup> DEMEREC, M.: Production of staphylococcus strains resistant to various concentrations of penicillin. Proc. Nat. Acad. Sci., 1945, xxxi, 16.

## REVIEWS

*Practical Physiological Chemistry.* By PHILIP B. HAWK, Ph.D., President, Food Research Laboratories, Inc., BERNARD L. OSER, Ph.D., Director, Food Research Laboratories, Inc., and WILLIAM H. SUMMERSON, Ph.D., Associate Professor of Biochemistry, Cornell University Medical College. Twelfth Edition. 1323 pages; 23.5 × 16 cm. 1947. The Blakiston Company, Philadelphia. Price, \$10.00.

The twelfth edition of *Practical Physiological Chemistry* follows the eleventh after 10 years and marks the fortieth year since the first edition by Hawk and Bergheim. Two new authors, Oser and Summerson, have joined the senior author with this edition and a group of authorities in various biochemical fields has assisted in the revision of the material in a number of chapters.

The past 10 years have been characterized by many advances in biochemical fields. Many of these are reflected in the revisions and additions to the clinical and theoretical aspects of the subject as well as in the choice of technical material. About half of the 36 chapters have undergone major revisions and one new chapter on antibiotics has been added. Much of the obsolete material has been deleted and new sections have been added on Warburg tissue slice technic, on the polarograph, electrophoretic fractionation of proteins, photometric and fluorimetric analysis and microbiological estimation of various amino acids and vitamins. The volume has been increased in size by over 350 pages.

The section on methods is good. Usually a number of alternate procedures are presented for the determination of a substance. Occasionally, however, a single method, not always too well known, is given alone. The appendix contains useful information of the preparation of solutions; tables on the composition of foods; and a section on the care of animals for nutritional experiments.

This edition should enjoy the same popularity as earlier ones, both as a textbook and as a reference volume for the clinical laboratory.

M. A. A.

*Clinical Hematology.* By MAXWELL M. WINTROBE, M.D., Ph.D., Professor of Medicine, University of Utah School of Medicine. 2nd Edition. Illustrated with 197 engravings and 14 plates, 10 in color. 862 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$11.00.

There is no doubt that this volume is well on its way to establishing itself as a classic text in its field. The second edition, released for publication in October, 1946, displays evidence of careful revision throughout. The few years intervening between publication of the first edition and the present one have seen many important advances in hematology, most of which are accorded scholarly and comprehensive consideration here. Among the new material is an account of the discovery of the chemical structure, synthesis and use of "folic acid"; consideration of the implications and use of the nitrogen mustards in the lymphomata and leukemias; the rôle of the Rh factor in the etiology of erythroblastosis fetalis and hemolytic transfusion reactions. An entirely new chapter dealing extensively with the chemical metabolism of the erythrocyte and related pigment metabolism has been added. A feature of great value to the reader interested in pursuing a particular topic is the extensive and well-chosen bibliography. The book is highly recommended.

M. S. S.

*Methods of Vitamin Assay.* Prepared and Edited by THE ASSOCIATION OF VITAMIN CHEMISTS, INC. 189 pages; 23.5 × 16 cm. 1947. Interscience Publishers, Ltd., London. Price, \$3.50.

"Methods of Vitamin Assay" is the result of the efforts of a group of chemists who formed an Association of Vitamin Chemists in 1943. Their aim was to promote "(1) the exchange of information on methods of vitamin analysis for specific food, feedstuffs, and pharmaceutical products; (2) the consideration of means of improving vitamin methods from the standpoint of cost, simplicity, and optimum correlation with the vitamin requirements of man; (3) a better interpretation of the significance of vitamin values, as determined by various methods." Members of this group together with other authorities submitted information on analytical technics, both published and unpublished, to a general methods committee who then chose one general method for each type of analysis which could be applied to the vitamin to be determined. These procedures are given in great detail with the assumption that they are to be carried out by laboratory technicians with a limited training in quantitative analysis. Procedures for vitamin A, carotene, riboflavin, niacin and ascorbic acid are given. References to methods for 10 other vitamins are also included.

Although many of the methods are applicable to the analysis of blood and urine, specific modifications are not always included in the extensive notes. This somewhat limits the usefulness of the methods for the usual hospital technician. The volume should prove invaluable, however, to all those interested in vitamin assay, and it should do much to standardize the methods of sampling and vitamin analysis of food and pharmaceutical products.

M. A. A.

#### BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Atlas of Cardiovascular Diseases: Correlation of Clinical Electrocardiography and Cardiac Roentgenology with Clinical History and Autopsy Findings.* By IRVING J. TREIGER, M.D., Assistant Professor of Medicine, University of Illinois, Chicago, etc. 180 pages; 30 × 22 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$10.00.

*Curare: Its History, Nature and Clinical Use.* By A. R. MCINTYRE, Ph.D., M.D., Professor of Physiology and Pharmacology, College of Medicine, The University of Nebraska. 240 pages; 24.5 × 17.5 cm. 1947. The University of Chicago Press, Chicago. Price, \$5.00.

*Diagnosis and Treatment of Diarrheal Diseases (The).* By WILLIAM Z. FRADKIN, A.B., M.D., Assistant Attending Gastroenterologist, Jewish Hospital of Brooklyn, etc. 254 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, \$6.00.

*Gynecology, With a Section on Female Urology (2nd Edition).* By LAWRENCE R. WHARTON, Ph.B., M.D., Assistant Professor of Gynecology, The Johns Hopkins Medical School, etc. 1027 pages; 25 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$10.00.

*Health and Rehabilitation Through Chest Training.* By SAMUEL DELANO, A.B., M.D., Harvard. 142 pages; 22.5 × 14.5 cm. 1947. The William-Frederick Press, New York. Price, \$2.50.



- Manual of the Common Contagious Diseases (A)* (4th Edition). By PHILIP MOEN STIMSON, A.B., M.D., Associate Professor of Clinical Pediatrics, Cornell University Medical College, etc. 503 pages; 20 × 13.5 cm. 1947. Lea & Febiger, Philadelphia. Price, \$4.00.
- Methods of Diagnosis*. By LOGAN CLENDENING, M.D., F.A.C.P., Late Professor of Clinical Medicine and History of Medicine, University of Kansas School of Medicine, and EDWARD H. HASHINGER, M.D., F.A.C.P., Professor of Clinical Medicine, University of Kansas School of Medicine. 868 pages; 25 × 17.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$12.50.
- Microbial Antagonisms and Antibiotic Substances*. (Revised Edition.) By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers University, etc. 415 pages; 24.5 × 16 cm. 1947. The Commonwealth Fund, New York. Price, \$4.00.
- Office Immunology, Including Allergy: A Guide for the Practitioner*. Edited by MARION B. SULZBERGER and RUDOLPH L. BAER. 420 pages; 21 × 14.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, \$6.50.
- Paravertebral Block in Diagnosis, Prognosis, and Therapy: Minor Sympathetic Surgery*. By FELIX MANDL, M.D., F.I.C.S., Professor of Surgery, Hadassah University Hospital, Jerusalem. Translated by GERTRUDE KALLNER, M.D. 330 pages; 23.5 × 15.5 cm. 1947. Grune & Stratton, Inc., New York. Price, \$6.50.
- P-Q-R-S-T: A Guide to Electrocardiogram Interpretation* (2nd Edition). By JOSEPH E. F. RISEMAN, M.D., Associate in Medicine, Harvard Medical School, etc. 84 pages; 14.5 × 21.5 cm. 1947. The Macmillan Company, New York. Price, \$3.50.
- Rocky Mountain Conference on Infantile Paralysis*. Sponsored by THE UNIVERSITY OF COLORADO SCHOOL OF MEDICINE AND HOSPITALS and THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS, INC. 199 pages; 27.5 × 21.5 cm. (Paper). University of Colorado, School of Medicine and Hospitals, Denver. Price, \$1.25.
- Vascular Disorders of the Limbs, Described for Practitioners and Students* (2nd Edition). By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London, etc. 118 pages; 22.5 × 15 cm. 1947. The Macmillan Company, New York. Price, \$2.25.
- Psychiatric Research*. Papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hospital, Waverley, Massachusetts, May 17, 1946, by CECIL K. DRINKER, JORDI FOLCH, STANLEY COBB, HERBERT S. GASSER, WILDER PENFIELD and EDWARD A. STRECKER. 113 pages; 22 × 14.5 cm. 1947. Harvard University Press, Cambridge. Price, \$2.00.

## COLLEGE NEWS NOTES

### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948–June 30, 1949. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from \$2,200 to \$3,000.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

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### AUTUMN MEETING, BOARD OF REGENTS AND COMMITTEES

The regular autumn meeting of the standing committees and of the Board of Regents of the College will be held at the College Headquarters, Philadelphia, November 22–23, 1947.

The Committee on Credentials will consider only those candidates who have been formally proposed and their credentials completely filed sixty days in advance thereof, or by September 23.

All other matters requiring the attention of the Board of Regents should be submitted adequately in advance of November 21.

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### COMMITTEE ON MASTERSHIPS APPOINTED BY THE PRESIDENT

Among the amendments to the By-Laws adopted at the 28th Annual Session of The American College of Physicians, was one providing for a Committee on Master-ships to be named by the President for the specific purpose of making nominations of Masters to the Board of Regents for election or rejection. The Mastership Committee shall consist of two members from the Board of Regents and one member from the Board of Governors. President Hugh J. Morgan has announced the appointment of the following Mastership Committee:

William S. Middleton (Chairman), Madison, Wis.

Walter B. Martin, Norfolk, Va.

Lewis B. Flinn, Wilmington, Del.

A Master shall be one who has attained the rank of Fellow and who on account of personal character, positions of influence and honor, eminence in practice or medical research, or other attainments in science or in the field of medicine, is recommended to the Board of Regents for special and well-earned distinction.

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### EASTERN PENNSYLVANIA REGIONAL MEETING

The annual Regional Meeting for Eastern Pennsylvania members of the College will be held in Philadelphia, Friday, November 21, under the direction of Dr. Edward L. Bortz, Governor. The program will be announced later, but the meeting will be held in conjunction with a postgraduate course in Gastro-enterology to be given in

Philadelphia from November 17 to 26 under the auspices of the College, with Dr. Henry L. Bockus as Director. Luncheon will be served at the College Headquarters, and the afternoon and evening sessions will be held at the Warwick Hotel, 17th and Locust Streets, Philadelphia.

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#### NEBRASKA REGIONAL MEETING

The annual Regional Meeting for members of the College in Nebraska will be held at Lincoln on September 20, under the Governorship of Dr. Joseph D. McCarthy, F.A.C.P., Omaha. Members of the College from Lincoln will act as hosts. The program of the meeting will be printed and distributed to members throughout the state about the first of September.

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Marking the twentieth anniversary of the founding of Georgia Warm Springs, a three-day clinical conference on diagnosis and treatment of poliomyelitis will be held at Warm Springs, Georgia, on September 15, 16, and 17.

Physicians interested in attending this conference should make inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5, N. Y. Complete program of the meeting will be available on request.

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#### SECOND ANNUAL POSTGRADUATE COURSE IN DISEASES OF THE CHEST

The American College of Chest Physicians is sponsoring a second annual postgraduate course in diseases of the chest to be held during the week of September 15-20, 1947, at the Municipal Tuberculosis Sanitarium, Chicago, Illinois. The emphasis in this course will be placed on the newer developments in all aspects of diagnosis and treatment of diseases of the chest.

The course will be limited to 30 physicians. Tuition fee is \$50.00. Further information may be secured at the office of the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

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The American Association for the Study of Goiter, of which Dr. James H. Means, F.A.C.P., Boston, is President, will hold its 1948 meeting at the King Edward Hotel, Toronto, Can., May 6, 7, and 8, 1948. The program will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

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Major General Norman T. Kirk, (MC), USA, F.A.C.P., and former Surgeon General, has been awarded the Typhus Commission Medal in recognition of the outstanding contributions he made to the work of the Commission.

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Dr. Paul R. Hawley, F.A.C.P., Medical Director of the Veterans Administration, is the recipient of the Gorgas Award for 1947. This award, sponsored by Wyeth, Inc., is presented each year to a physician who has contributed signally to the field of military medicine.

The Distinguished Service Medal has been bestowed on Dr. Hawley for his exceptionally effective activities as Chief Surgeon in the European Theater of Operations, June, 1944, to May, 1945.

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Dr. J. C. Geiger, F.A.C.P., San Francisco, has been honored by the award of the Crown of Orange Nassau, Officer Grade, by the Queen of Holland.

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Brigadier General Edward A. Noyes, (MC), USA, F.A.C.P., has received the Legion of Merit for his successful development of special facilities for the care and

rehabilitation of patients while Service Command Surgeon of the Fifth Service Command, July, 1944, to September, 1945.

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Colonel Edgar E. Hume, (MC), USA, F.A.C.P., is a recipient of the Typhus Commission Medal, given in recognition of his meritorious service during the 1943-44 epidemic of typhus in Naples.

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The Legion of Merit has been awarded to Colonel William D. Graham, (MC), USA, F.A.C.P., to note his exceptional accomplishments as Commanding Officer of the 158th General Hospital, England, November, 1944, to July, 1945.

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Captain Louis H. Roddis, (MC), USN, F.A.C.P., has been awarded the Navy Commendation Ribbon. The citation mentions his "invaluable consultation service," and his achievements in "disease prevention and evacuation of the sick and wounded."

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Dr. Matthew Molitch, F.A.C.P., Atlantic City, N. J., and formerly Lieutenant Colonel in the A.U.S., is a recipient of the Army Commendation Ribbon. The citation refers to Dr. Molitch's contributions to the service while neuropsychiatric consultant at Fort Knox, January, 1944, to January, 1946.

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Lieutenant Colonel Wayne G. Brandstadt, (MC), USA, F.A.C.P., has been awarded the Bronze Medal for his superior achievements in the management of battle casualties while Commanding Officer of the 53rd General Hospital, England, August 1, 1944, to May 8, 1945.

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The Typhus Commission Medal has been given to Dr. David H. Clement, F.A.C.P., New Haven, Conn. Formerly a Major in the A.U.S., Dr. Clement is said to have improved methods of treatment of typhus fever while Surgeon in charge of the Commission's ward in the 116th Evacuation Hospital, Dachau, Germany, May-June, 1945.

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Colonel William B. Foster, (MC), USA, (Associate) has been awarded the Legion of Merit for his exceptional accomplishments as a member of the Secretary of War's Separation Board, January, 1944, to February, 1946.

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On June 30, Dr. Francis G. Blake, F.A.C.P., 2nd Vice President of the American College of Physicians, retired from the Deanship of the Yale University School of Medicine. His successor is Dr. C. N. H. Long, Sterling Professor of Physiologic Chemistry.

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Dr. John D. Van Nuys has been appointed Dean of the Indiana University School of Medicine.

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Dr. Robert C. Page, F.A.C.P., New York, N. Y., has recently given the College a copy of "A Biometric Study of Ten Years Medical Service," published as Number 1, Volume 7, of The Medical Bulletin by Standard Oil Company (New Jersey) and Affiliated Companies.

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Dr. William C. Menninger, F.A.C.P., Topeka, Kans., has been elected to the position of President-elect of the American Psychiatric Association.

## PROPOSED ARMY MEDICAL RESEARCH AND GRADUATE TRAINING CENTER

The Army is planning to build a large medical center at Forest Glen, Md., outside Washington, D. C. It will comprise an Institute of Pathology building, a 1,000-bed general hospital, an Institute of Medicine and Surgery building, laboratory buildings, and an administration building which will contain an auditorium, research library and teaching facilities, as well as the Army Medical Museum. The Institute of Medicine and Surgery building will house the departments of Research Medicine, Research Dentistry, Veterinary Medicine, Research Surgery, X-Ray and Radiation, and Preventive Medicine. The plans include provisions for an animal farm and quarters for the staff.

Various Army units, now located elsewhere, will be brought to this center: the Medical Nutrition Laboratory, from Chicago; the Medical Field Research Laboratory, from Fort Knox; and the Surgical Research Unit, from Fort Sam Houston.

The hospital will have 200 of its 1,000 beds specifically allocated to research, and is so planned as to be capable of expansion to provide 1,500 beds.

The initial cost of the center is estimated to be \$40,000,000.

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UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL OFFERS POSTGRADUATE COURSE  
IN PSYCHIATRY AND NEUROLOGY

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical School, San Francisco 22, Calif., announces that a postgraduate course in psychiatry and neurology will be offered at the Langley Porter Clinic of the University of California Medical Center for a period of twelve weeks, September 8 to November 28, 1947. Instruction will be under the direction of Dr. Karl M. Bowman, professor of psychiatry in the University of California Medical School.

Registration is open to graduates of approved medical schools, and the number of registrants will be limited to sixty. Fee, \$200.

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## CORRECTION

*In figure 1, page 192, of the article "Medicine in the European Theater of Operations" by Dr. William S. Middleton (February 1947 issue), the name of Lt. Colonel Benjamin H. Rutledge was inadvertently omitted from the list of Hospital Center Consultants by the author who has requested that this note of correction be made.*

## MINUTES, BOARD OF GOVERNORS

CHICAGO, ILL.

APRIL 28, 1947

The first meeting of the Board of Governors during the 28th Annual Session of the American College of Physicians convened at the Palmer House, Chicago, at 5:00 p.m., April 28, 1947, with Dr. C. W. Dowden, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary. The following members were in attendance:

Oliver C. Melson	Arkansas
Ernest H. Falconer	California (Northern)
Benjamin F. Wolverson	Iowa
Edgar Hull	Louisiana
Douglas Donald	Michigan
Edgar V. Allen	Minnesota
Ralph Kinsella	Missouri
Harry T. French	New Hampshire
George H. Lathrope	New Jersey
Paul F. Whitaker	North Carolina
Robert B. Radl	North Dakota
Hugh A. Farris	Maritime Provinces
Arthur T. Henderson	Quebec
E. Dice Lineberry	Alabama
Fred G. Holmes	Arizona
Lewis B. Flinn	Delaware
Turner Z. Cason	Florida
Samuel M. Poindexter	Idaho
Walter L. Palmer	Illinois (Northern)
C. W. Dowden (Chairman)	Kentucky
Eugene H. Drake	Maine
Wetherbee Fort	Maryland
John G. Archer	Mississippi
Ernest D. Hitchcock	Montana and Wyoming
Asa L. Lincoln	New York (Eastern)
Joseph N. Ganim (Alternate)	Ohio
T. Homer Coffen (Alternate)	Oregon
M. D. Levy	Texas
Karver L. Puestow	Wisconsin
Ramon M. Suarez	Puerto Rico
John W. Scott	Alberta, British Columbia, Saskatchewan and Manitoba
Leland P. Hawkins	California (Southern)
W. B. Yegge (Alternate)	Colorado
A. B. Landry (Alternate)	Connecticut
Wallace M. Yater	District of Columbia
Cecil M. Jack	Illinois (Southern)
Harold H. Jones	Kansas
Chester S. Keefer	Massachusetts
Joseph D. McCarthy	Nebraska
Edward C. Reifenstein, Sr.	New York (Western)
Wann Langston	Oklahoma

Edward L. Bortz (Vice Chairman)	Pennsylvania (Eastern)
R. R. Snowden	Pennsylvania (Western)
John L. Calene	South Dakota
Louis E. Viko	Utah
Henry C. Gotshalk (Alternate)	Hawaii
Herbert K. Detweiler	Ontario
Gilbert M. Stevenson	Republic of Panama and the Canal Zone
Ex Officiis:	
Col. H. C. Dooling (Alternate)	United States Army
Adm. C. A. Swanson	United States Navy
O. L. Anderson (Alternate)	United States Public Health Service

Abstracted minutes of the previous meetings of the Board of Governors were read by the Secretary, and approved as read.

Chairman Dowden addressed the board briefly, reminding the members that he had circularized the entire Board by letter concerning the proposed amendments to the By-Laws affecting the eligibility of new members, and having received no replies, he felt justified in assuming that the Board of Governors wholly agreed to the proposed changes.

The Secretary, Mr. Loveland, read several communications from Governors who were unable to be present due to unusual circumstances. The death of Dr. J. O. Arnson, Governor for North Dakota, was noted, and the Board arose and observed a moment of silence.

The Secretary reported on proceedings of the Board of Regents at its meeting the day previous, covering those points of particular interest to the Board of Governors. These included: first, an amendment to the By-Laws providing that the maximum tenure of office of a Governor in the future shall be three terms of three years each; second, revision and restatement of the requirements for membership, with particular reference to Associates who fail to complete the requirements for Fellowship in the specified period of five years. There followed a general discussion of the subject of tenure of office of Governors, during which it was brought out that the new rules will probably be retroactive, and that none of the present Governors shall serve a longer period than three consecutive full terms of three years each; also that short terms as Acting Governors, or partial terms to fill out the unexpired term of a former Governor, will not be counted against the three full terms to which the incumbent may be entitled.

At this point, Dr. Wolverton discussed the manner of the election of Governors, suggesting that the American College of Physicians had never presumed to be a strictly democratic organization, but that the Fellows in any territory concerned should be polled in order that they may have some opportunity to express a preference for the Governor of their region. It was pointed out that the Nominating Committee is instructed by the By-Laws to give due consideration to suggestions of members from the respective states, provinces or districts, which will be represented by nominees if elected. Dr. Wolverton, however, felt that a definite routine should be established by which there would be an actual poll of the members in each state, the preference of each individual Fellow to be sent to the Executive Secretary, and the results turned over to the Nominating Committee to be used as a guide in making nominations.

Dr. Allen proposed that the Fellows in any state should have the right to elect by ballot their Governor, and that the members of the Board of Regents be elected by the Board of Governors; also that the President and Officers of the College likewise, by the Board of Governors. He felt this would bring the College in line with the truly representative organization that he felt it should be. He felt the present mechanism of merely allowing the Fellows to make recommendations to the Chairman of the Nominating Committee is a long way removed from a truly democratic system.

Chairman Dowden pointed out that this would entail a change in the By-Laws, and expressed a desire to have Dr. Wolverton and Dr. Allen submit their resolutions in writing, whereupon they will be presented to the Board of Regents for consideration, or to be more clearly presented to the Board of Governors for recommendation to the Board of Regents.

Dr. Levy, Governor for Texas, pointed out that in that state, where they have from 250 to 300 members scattered over a vast territory, it would be difficult for the men to select candidates, due to the isolation of one group from another, and the absence of any fairly intimate acquaintanceships over the state as a whole. He did not feel that a poll of the members by mail would produce the results desired. Such a plan had already been resorted to in some instances, and instead of getting any clear-cut selections of candidates, there has been a large number of candidates suggested, and in some instances, members have proposed their own names as candidates.

Dr. Palmer proposed, if this plan shall be tried, that they use the so-called Hare System, by which the complete list of Fellows would be furnished to the men in a particular state, and they would be asked to make nominations. There could be ten or fifty such nominations, and this list again may be sent to the same Fellows with the request that they vote in the order of first preference.

Dr. Holmes said that this method was used in elections in the Kiwanis Club for years, for the election of President, and that it necessitated polling several times. Dr. Holmes proposed that three top men for election would be more practical.

In extended discussion, a motion was made by Dr. Levy, and seconded by Dr. Hull, to proceed according to the various discussions advocated by Drs. Wolverton and Allen; Dr. Kinsella asked specifically for the wording of the motion, and the clarification of the statements therein. The reporter read the discussion, but confusion still remained, and many Governors expressed fear that any proposal, unless clearly worded and carefully organized, would lead to political manipulation in the election of the Officers, Regents, and Governors of the College.

Eventually, all motions were withdrawn, and Dr. Whitaker moved that a committee of five be appointed by the Chairman of the Board of Governors to study and to bring in some procedure for election of the members of the Board of Governors that will be satisfactory to the group as a whole.

The motion was seconded by Dr. Fort, put to vote, and carried.

Chairman Dowden appointed Dr. Allen, Chairman, Drs. Wolverton, Palmer, Levy, and Hull, and asked them to bring in their report at the next meeting of the Board of Governors.

Dr. Wolverton asked for some guidance, inquiring whether Associates should or should not have a voice in the election of Governors. It was pointed out by the Secretary that the By-Laws of the College definitely state that an Associate occupies purely a probationary status, and is entitled to no vote.

Chairman Dowden called upon Mr. Loveland to present the report of the Executive Secretary. Mr. Loveland stated that his full annual report would be given at the general business meeting of the College later in the week, and that since all Governors presumably will be in attendance, he would not repeat that portion of his report concerning finances, regional meetings, the Annals, membership data, etc.

He reminded the Board that the names of all candidates elected to Associateship or Fellowship had already been posted on the bulletin board; he discussed the problem of getting proposals filed adequately in advance—at least thirty days before action is required, and reminded the Board that under the new regulations, this period of time would be extended in the future to sixty days. He assured the Board that they would receive individual reports on all candidates who had been deferred or rejected. He explained that it had not been possible to publish a new and complete Directory of the College, due to paper and labor shortages, and excessive costs. In its place, a new Membership Roster had been published during January, 1947, and subject to the advice of the Board of Regents, a complete Directory would be published in the future.



The report of the Executive Secretary was accepted by resolution.

Dr. E. L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, reported that during 1946, the College conducted 23 postgraduate courses, with a total registration of 1,208 physicians, chiefly members of the College. He said the courses have been growing in popularity, and there has been a substantial improvement in the caliber of teaching. Whereas some years ago the Committee often had difficulty in interesting teachers and faculties of medicine to put on these courses for the College, his Committee now receives many offers from top flight individuals and institutions to participate in the College program. An attempt has been made to place the College courses at points over the country where the faculties are adequate to the needs of the College. The College has been as generous as possible with non-members in permitting them to attend the courses, but the demand from members in many instances has exhausted the facilities, and non-members could not be accommodated.

Dr. Bortz said the Committee considers the ideal size for the course to be 25 to 35, but the demand for the College courses has been so great that the size of the classes has had in many instances to be doubled or tripled. Some courses are already subscribed to one or more years in advance.

Dr. Bortz reviewed the proposed courses for the autumn of 1947 and the spring of 1948. He reported that the Committee, with the approval of the Board of Regents, had increased the registration fee from \$20 to \$30 per week, \$25 of which will be turned over to the director or institution, and \$5 of which will be withheld to be used by the College to help defray administrative expenses of arranging the courses. He emphasized also that the Committee proposes to have more instruction in the basic sciences than heretofore, and to enter into the newer work in the field of nucleolar physics and radioactive materials, etc. Dr. Bortz further reported that several other medical organizations have consulted the Committee and the Executive Secretary, considering ways and means of employing our type of program. He said it is significant that many faculties of medicine are leaning to this type of instruction, which concentrates material in such a way that men can get a great deal in a very short period of time.

(On motion by Dr. Allen, seconded and regularly carried, the report of the Advisory Committee on Postgraduate Courses was accepted.)

The Secretary, Mr. Loveland, reported that the Committee on Credentials had recommended to the Board of Regents and the Board of Regents had approved a new system of receiving votes from Fellows on new candidates, supplanting the card inquiry system in use for many years. The new plan provides that proposals shall be filed at least 60 days in advance of action; that the names shall be submitted in a geographical printed roster of candidates to all Fellows and Masters of the College, with requests for reports, whether favorable or unfavorable, on each candidate from the Fellows' or Masters' territory. The card system had become top-heavy, he said, in that it required the distribution of between 50,000 and 75,000 cards per annum, for which both forward and return postage was required, and with much expense involved for printing, filing, and so forth. The new system will provide a far more effective, less expensive, and more adequate plan, it was claimed by the Committee on Credentials.

In the discussion that followed, it was pointed out that this system does not in any way interfere with the present routine of many Governors, by which a consulting committee is maintained to help advise the Governor before he endorses a candidate. The appointment of such consulting committees is a matter that is entirely in the hands of the Governor, for his personal guidance. Information received through the card inquiry system, and sometimes on proposal forms themselves, often proved inadequate. Dr. Lathrope of the Committee on Credentials appealed to the Governors to take more care in seeing that full and complete data concerning every candidate's background,

experience, present appointments, and present activities, are always recorded for the assistance of the Committee on Credentials.

Chairman Dowden made an announcement concerning the agenda of the next meeting of the Board and other matters that should be submitted to the Governors for consideration.

Adjournment—6:20 p.m.

Attest: E. R. LOVELAND

*Secretary*

## MINUTES, BOARD OF GOVERNORS

CHICAGO, ILL.

APRIL 30, 1947

The second meeting of the Board of Governors during the 28th Annual Session of The American College of Physicians convened at the Palmer House at 1 p.m., April 30, 1947, with Dr. C. W. Dowden, Chairman, presiding, and Mr. E. R. Loveland acting as secretary. The following were in attendance:

Oliver C. Melson	Arkansas
Ernest H. Falconer	California (Northern)
Benjamin F. Wolverton	Iowa
Edgar Hull	Louisiana
Douglas Donald	Michigan
Edgar V. Allen	Minnesota
Ralph Kinsella	Missouri
Harry T. French	New Hampshire
George H. Lathrope	New Jersey
Paul F. Whitaker	North Carolina
Robert B. Radl	North Dakota
Alexander M. Burgess	Rhode Island
Robert Wilson, Jr. (Alternate)	South Carolina
Paul K. French	Vermont
J. Edwin Wood, Jr.	Virginia
Charles E. Watts	Washington
Delivan A. MacGregor	West Virginia
Arthur T. Henderson	Quebec
E. Dice Lineberry	Alabama
Fred G. Holmes	Arizona
Lewis B. Flinn	Delaware
Turner Z. Cason	Florida
Samuel M. Poindexter	Idaho
Walter L. Palmer	Illinois (Northern)
C. W. Dowden (Chairman)	Kentucky
Eugene H. Drake	Maine
Wetherbee Fort	Maryland
John G. Archer	Mississippi
Ernest D. Hitchcock	Montana-Wyoming
Robert O. Brown	New Mexico
Asa L. Lincoln	New York (Eastern)
Joseph N. Ganim (Alternate)	Ohio
T. Homer Coffen (Alternate)	Oregon
M. D. Levy	Texas
Karver L. Puestow	Wisconsin
John W. Scott	Alberta, British Columbia, Saskatchewan and Manitoba

Leland P. Hawkins	California (Southern)
W. B. Yegge (Alternate)	Colorado
A. B. Landry (Alternate)	Connecticut
Wallace M. Yater	District of Columbia
Cecil M. Jack	Illinois (Southern)
Harold H. Jones	Kansas
Chester S. Keefer	Massachusetts
Joseph D. McCarthy	Nebraska
Edward C. Reifenstein, Sr.	New York (Western)
Edward L. Bortz (Vice Chairman)	Pennsylvania (Eastern)
R. R. Snowden	Pennsylvania (Western)
John L. Calene	South Dakota
William C. Chaney	Tennessee
Louis E. Viko	Utah
Henry C. Gotshalk (Alternate)	Hawaii
Herbert K. Detweiler	Ontario
Gilbert M. Stevenson	Republic of Panama and Canal Zone
Ex Officiis:	
Col. H. C. Dooling (Alternate)	United States Army
Capt. Frederick L. McDaniel (Alternate)	United States Navy
O. L. Anderson (Alternate)	United States Public Health Service
David P. Barr, President	
E. R. Loveland, Executive Secretary	

Reading of the minutes of the previous meeting was dispensed with.

CHAIRMAN DOWDEN: The President of the College, Dr. Barr, needs no introduction; we shall be happy to hear from him now.

PRESIDENT BARR: We had an opportunity to discuss our problems at the combined dinner meeting of the Regents and Governors on Sunday evening. I have nothing special to bring before you today.

Certainly no one can attend meetings such as we held in Philadelphia last year or the one we are having now without realizing the tremendous educational influence which this College has and can have. Many of us have the opportunity to see and to advise young men who want to be internists and who are arranging their entire lives for the next several years along the pattern which will enable them to qualify for certification and for Fellowship in this College. It goes farther than that. It is my belief that the internists are key people in the practice of medicine. Surgeons, in general, are pretty well occupied with technical procedures, also, general practitioners, as everyone knows; but internists, as a group, perhaps, do have a little more time to consider large problems of progress; they are interested in the broader phases of medicine.

I have had a growing realization of the tremendous responsibilities of this College. Now more than ever before, I feel this. The responsibility is something more than the mere setting of standards, or certification, or what we outline in black and white for preparation, but for positive education, for improvement of conditions of practice, for the better training of young men, for the enlarging of opportunities in residency. I am convinced that this is chiefly in the hands of the College. If the intent of the College is to be applied to the men who are going to be internists in this country, our influence must be exerted wholly.

The position of Governor has changed remarkably during the past few years, for at first it was more or less formal. The Governor's responsibilities, however, have rapidly expanded—he is responsible largely for new members; for advice in regard to certification; organization of regional meetings with their greatly increasing influence, etc. I think we are ready now to give more impetus to the work of the

Governor and the work in local districts to make the College work of a more positive educational value. The local or state meetings not only have the purpose of educating the Fellows who are present but extending certain training to men who will become Fellows later on.

I need not say that it has been a pleasure to be President of this organization; it has been a great privilege and a great honor and I shall retire with much greater convictions than I have had before of the great influence which the College has and can have. (Applause)

At this point, Chairman Dowden called on Dr. E. V. Allen, Chairman of the Committee appointed at the previous meeting, to give a report on proposals affecting the method of elections of Officers, Regents and Governors.

DR. ALLEN: This matter is a question of a more positive voice in the election of Governors by the Fellows in the respective states and territories. A motion was made at the last meeting of this Board, and withdrawn, that Governors be elected by direct vote of the Fellows of their geographic components. So much objection and discussion followed that the matter was referred to this Committee. The Committee has considered the matter at length. The first aspect of it is that there should be no change; the present situation is entirely satisfactory. The Committee itself is unanimous in the belief that the present situation is not satisfactory. The problem was then considered relative to the direct election of the Governor by the Fellows in his state or territory and it was felt that that was too great a step to take at the present time to have the support of the Committee.

Other alternatives were proposed. One was that the Fellows should be polled with regard to nominations of Governors, and the three names receiving the greatest number of votes should be submitted to the Nominating Committee for selection of a candidate.

The second alternative was that the Chairman of the Nominating Committee present to the Fellows of the various geographical components the names of three Fellows, and that the Fellows, themselves, would then select a Governor.

However, after consideration of these proposals in some detail, the Committee felt that the steps proposed should not be taken hastily; that we are not yet in shape to make a firm recommendation relative to this matter. Therefore, the Committee presents the following resolution:

"Whereas, It is desirable that the Fellows of The American College of Physicians of each State, District or Territory should have a voice in the selection of their Governor; and

"Whereas, The By-Laws (Article I, Section 3), provide that the selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members; and

"Whereas, The Chairman of the Board of Governors has appointed a Committee to consider the problem in the foregoing; and

"Whereas, Said Committee has met in session; and

"Whereas, It is the opinion of the Committee that more time is needed for adequate study; and

"Whereas, A change should not be made hastily and without consideration of the many factors involved; be it therefore

"Resolved, That the Chairman of the Board of Governors designate the present Committee or appoint a new Committee to study the problem with diligence and care and make appropriate recommendations to the Board of Governors, whereby the above mentioned By-Laws may be implemented; said recommendation to be presented to the Board of Governors meeting in session in 1948."

Mr. Chairman, I will move the adoption of this Resolution.

DR. CASON: I second the motion.

CHAIRMAN DOWDEN: The matter is open for discussion.

DR. YATER: Does the adoption of this Resolution preclude any form of democratic polling of members of a district by the Governor should he wish to attempt to submit some names for the consideration of the Nominating Committee?

CHAIRMAN DOWDEN: I think any information a Governor can give to the Nominating Committee will have weight. This present Committee should be continued, to make a further report in 1948.

DR. ALLEN: It is the hope of this Committee that it will receive an expression from the Governors and I think it would be wise for the Governors to take a formal or informal poll of their membership relative to what they desire. I wish to emphasize this is not required by the By-Laws, although there is a By-Law already set up for this, and so no change in the By-Laws is contemplated at all.

DR. LATHROPE: The question brought up at our previous meeting was on the basis of democratization of the College. Personally, I feel this College cannot be a pure democratic organization. Five thousand men scattered all over North America cannot do it. To my mind, it should be an autocracy, but we should have a little better machinery for controlling the autocratic set-up. The crux of this problem goes right straight to the Nominating Committee. I would like to recommend to this Committee, which I think is a very good Committee and an important one, the consideration of a recommendation in a change in the By-Laws regarding the Nominating Committee. At present, in Section 3, Article I "Duties of the President: 'He shall within one month after induction to office appoint two members from the Board of Governors, two members from the Board of Regents and one Fellow at large'" to form a Nominating Committee. There you have a tight-fisted, closed organization about which you can do nothing should a group want to take control.

Now, we haven't had that yet. We have had a splendid organization as long as I have known anything about the College, but it is right down the line. My suggestion would be that the Nominating Committee be an elective one; two members to be elected by the Board of Governors; two members to be elected by the Board of Regents; and they shall choose the fifth member.

DR. BURGESS: I should like to uphold the remarks of Dr. Lathrope. I think he has the right idea and this, followed out, will answer many of our objections, and still will not precipitate us into the troubles that we might get into if this matter were thrown open to allow for the political manipulations that in some areas would follow. I, therefore, urge that this special Committee give this suggestion consideration.

DR. BORTZ: A few years ago I was Chairman of the Nominating Committee, and we had a representative Committee. At no time was any member of the Committee approached by any member of the College to use his influence in any way in the selection of any nominee, either for the office of President or any of the other offices. I happen to know from members of other Nominating Committees, since then, that the Committees have been absolutely free of any approach by Officers of the College. They may have been approached by Fellows of the College with suggestions, but I think that sometimes the impression gets around that the President may appoint his friends on the Nominating Committee and that they hold a little secret conclave concerning who is to be nominated for office. I want to say that you can wipe that right off the slate, gentlemen, because any such impression is absolutely wrong.

I happen to know, also, that there have been Fellows of the College ambitious to become appointees to certain positions and that they have directly or indirectly approached certain members of the College and requested them to use their influence. That automatically removed that individual from any consideration of any nomination that the Nominating Committee might make. So, with all the faults and weak-

nesses, the Nominating Committee has not done too bad to date. I will say further that members of the Nominating Committee of which I was Chairman unofficially inquired around how various Fellows felt concerning proposed nominations. Not all Fellows in a particular region were polled, but there was a spot opinion obtained before the Committee went on record. Furthermore, the Committee made it a point to obtain the records of all proposed nominees, to study the records, the candidates' local positions with the Fellows, contributions to the College, etc. Observation of these men, their activities and participation in the work of the College after election, proved that the Committee was not far wrong in their selection. I would like to cite that a member of the Nominating Committee, when I was Chairman, who had served on other Nominating Committees and other positions, especially remarked that his experience with the College was extremely remarkable because no one was trying to manipulate the Committee. According to my experience, I cannot conceive of any nominations being conducted more fairly.

DR. LATHROPE: Mr. Chairman, I disclaim all criticism of anything that has gone on in the past. This organization has been carried on in a splendid and high-minded way up to date, but I am looking forward to twenty-five years from now when the College may have ten or twelve thousand members and might get into trouble then.

I would like to make another point: as a rule Fellows of the College are not too familiar with the responsibilities of the Governor, nor with the workings of the College. With a definite limitation on the term a Governor can serve, there will be every few years quite a good many new Governors elected to this Board. Would it not be a good thing for the new Governor to be elected a year preceding his taking office so that the man still in office can instruct him a bit in some of the details?

DR. WOLVERTON: Having started this original discussion, I should like to remark that I didn't mean democratization of the College from top to bottom; I had no such thought. I like to treat the College not as an autocracy but as a true aristocracy. The Fellows who control are the best men, and they control the best activities of the College and are the best men for that purpose. That is exactly as it should be. All that I had in mind was some mechanism whereby the Fellows in the respective geographical units would have more voice in indicating their preference for Governor so that there would be greater unanimity in the respective units and, perhaps, a better spirit.

DR. YEGGE: I am just an alternate Governor but it would seem to me that it would be a bit embarrassing to the Governor and to the members if he, himself, were to poll the state concerning his successor. If a state is to be polled, it should be done by the central office.

(The Resolution was put to vote as originally made by Dr. Allen's Committee and was carried.)

At this time, Chairman Dowden called for reports from Governors concerning their respective Regional Meetings during the past year.

Dr. Viko, Utah, had already reported on his meeting, March 29, before the Governors-Regents dinner meeting and had nothing to add.

Dr. Cason, Florida, reported a Regional Meeting held in Miami, November 3-4, 1946, in which the states of Alabama and Georgia participated. Dr. Cason asked that the new Governor for South Carolina contact him with a view to that state joining with the Southeastern states in their Regional Meetings. The Miami meeting had been well attended, the program was excellent and the results gratifying. Dr. Cason announced the next Regional Meeting for the area to be held in Tampa on or about December 5, 1947, that the plan of the meeting is being enlarged and on this occasion all Governors of the College will be especially invited, that a trip to Havana is planned immediately following the meeting in order to participate in the official formation of the new Cuban chapter of the College of which Dr. Centurion will be

named Governor. Dr. Cason said that a scientific program would take place on Monday and Tuesday and that the trip to Cuba should start on Wednesday. He further reported that the Governor for Puerto Rico had announced their state meeting there the following week and had extended an invitation to all Fellows interested to come to Puerto Rico from Cuba.

Dr. Fort, Maryland, reported the first tri-state Regional Meeting, Delaware, Maryland and District of Columbia, with invitations to West Virginia, North Carolina and Virginia, had been held at Baltimore, April 5, and through the coöperation of the University of Maryland and Johns Hopkins Hospitals, a most successful meeting had been held. The morning program was conducted at the University of Maryland Hospital, a luncheon was held at the Phipps Clinic Building at Johns Hopkins and the afternoon scientific session conducted in Hurd Memorial Hall at Johns Hopkins.

Dr. Lineberry, Alabama, reported that they had held their first Regional Meeting in Alabama at Birmingham on February 8, 1947. Not only had there been an excellent program, but the meeting contributed a great deal to broader acquaintanceships within the state. The scientific session had consisted of a series of fifteen-minute papers starting at 8:30 and concluding at 5:30 in the afternoon, followed by a dinner meeting. Dr. Lineberry advocated planning and announcing meetings earlier and also advocated that the state meetings be continued.

Dr. Walter L. Palmer, Northern Illinois, reported a Regional Meeting in Chicago on November 16, embodying Illinois, Indiana, Kentucky, Iowa, Michigan, Minnesota and Wisconsin. A wealth of material is available in that district, a most excellent scientific program was received with great enthusiasm and the attendance was between four and five hundred.

Dr. Reifenstein, Western New York, reported a Sectional Meeting of Western New York at Syracuse during the autumn of 1946; the meeting was well attended, the program well received. The Committee on Arrangements selected speakers primarily from the University of Buffalo, University of Rochester and the University of Syracuse. All the members had expressed the desire to have a Regional Meeting annually. He further stated that growing out of the experience of this Regional Meeting will be a request to have the territory of Western New York extended to include all of Northeastern New York down to and including Albany and following a border line from Albany to Binghamton, because all men in this territory will be more interested in the Regional Meetings in Western New York than in meetings held around New York City for Eastern New York.

Dr. Harry T. French, New Hampshire, reported that the New England Regional Meeting had been held at Hanover, New Hampshire, on January 28, 1947, with a gratifying program and attendance.

Dr. Paul K. French, Vermont, announced that the next New England Regional Meeting is being planned for Burlington in the autumn of 1948 and that invitations will be sent also to the Maritime Provinces and Quebec. Incidentally, Montreal is only one hundred miles removed from Burlington.

Dr. Chaney, Tennessee, reported a state meeting for Tennessee at Memphis on November 22, 1946. It was a one-day meeting at which several distinguished guests were on the program. The meeting proved exceedingly popular from the great host of letters of commendation received thereafter. Dr. Chaney said that the value of these meetings lies not only in their educational phase but in the opportunities presented to get acquainted with the internists in the whole region.

Dr. McCarthy, Nebraska, reported that several years ago state meetings were held immediately following the Annual Session of the College at which the meeting and important papers and clinics were reviewed. On March 29, 1947, the State of Nebraska held a state meeting at Omaha with every member in attendance with the exception of three. Prospective candidates for Associateship were invited to attend

as guests so that Fellows could observe them and get acquainted. A scientific session had been held in the afternoon, with papers presented by Fellows of the College who are on the faculties of the two medical schools. He advocated that these state meetings be used as a proving ground for younger men, both from the standpoint of the work they are doing and also the presentation thereof. Dr. McCarthy asked for advice with regard to whether the policy shall be to hold multi-state regional meetings or individual state meetings.

Chairman Dowden replied saying he felt it purely up to the state and the local circumstances. If a group of states desire to join, it is perfectly all right, or, if individual states desire to organize their own more personal meetings, it meets with the complete approval and cooperation of the College generally. However, the Board of Regents has been inclined to encourage the return to the state type of meeting rather than the extension of the very large multi-state regional meetings, except where special conditions warrant.

Dr. Bortz reported a meeting for Eastern Pennsylvania at Philadelphia on February 7, 1947, with the participation of members from New Jersey and Delaware, and with numerous guests from Western Pennsylvania and New York. He said that he feels the type of meeting, whether state or multi-state, depends upon the number of members available. States with small membership obviously should join with nearby territories, thus to make the meetings adequate. In Eastern Pennsylvania, Dr. Bortz uses the Regional Meeting as a proving ground for some of the younger members. Large committees of younger men are appointed and younger men of greater promise are placed on the program, especially Associates of the College. It gives them an opportunity to show what they are doing and also serves as a great stimulus, when they see that the College does not strictly limit its programs to the older men of great prominence and accomplishment. Incidentally, this gives the Governor a better knowledge of talent among the younger men and helps him in making recommendations to the Chairman of the Annual Session for papers from the local area. At the Philadelphia Regional Meeting, it has been customary to give a buffet luncheon, as a routine matter, to allow the visiting members to see and visit the College Headquarters. At the scientific program, Dr. Bortz usually asks other men to preside, men outside of the Philadelphia area, and in this manner, Fellows from other parts of the region feel that they become a more active part of the College. In the evening, the program is light and convivial, with no too serious talks. Every year the meetings are growing in size and popularity.

Dr. Whitaker, North Carolina, reported a Regional Meeting for that state at Winston-Salem on October 18, 1946. North Carolina has established the policy of alternating the meetings between Chapel Hill, where the University of North Carolina Medical School is located, and Winston-Salem, where the Bowman Gray School of Medicine is located. A five-man program committee is appointed annually and an attempt is made to establish membership interest throughout the state. Some meetings have taken the form of a symposium on certain phases of internal medicine while others have been didactic papers with clinics and demonstrations added. Furthermore, the state of North Carolina often joins the surrounding territories, such as the District of Columbia, Virginia and other states, in their regional meetings. Dr. Whitaker, too, inquired further about the policy of the College with regard to strictly state or multi-state meetings.

Dr. J. Edwin Wood, Jr., Virginia, reported a state meeting held at Richmond on February 19, 1947, which had been the best attended of any previous meeting. He advocated that the College or the Board of Governors formulate a definite policy with regard to the type of meeting to be held in the future, expressing the opinion that the type of meeting probably must be dependent somewhat upon the medical population of the state. In general, Dr. Wood felt that the individual state meetings, with the fellowship that goes with them, are the best type.



Dr. John Archer, Governor for Mississippi, reported that the State of Mississippi has only twenty members of the College and that heretofore they have been included within the Sectional Meeting for Tennessee, Arkansas, Louisiana and East Texas. In Mississippi, Dr. Archer has developed the plan of having an annual luncheon at the annual Mississippi State Medical Society meeting. At these luncheons practically all Mississippi members of the College are in attendance. A guest speaker is engaged and, in some instances, this guest speaker has been the College Governor for one of the neighboring states. Such a luncheon meeting was planned during the Mississippi State Meeting at Biloxi in May, 1947. The luncheons afford an opportunity for the members to get together, to know each other better and to discuss younger men in the state who may be aspiring to Associateship.

Dr. E. Dice Lineberry, Governor for Alabama, at this point, pointed out that some of the larger sectional meetings might be revised to advantage with respect to their territories, providing the organizing Governor's feelings would not be hurt. In the case of Alabama, the members had found it a little more convenient and attractive to attend the Sectional Meeting at Memphis rather than join in the Sectional Meeting in Florida.

An inquiry was made as to whether or not there are any states or provinces which are not included in some regional meeting set-up, and the Secretary, Mr. Loveland, reported that there are several such states and provinces not yet so included.

Chairman Dowden pointed out that there is nothing compulsory about a state or province holding a regional or sectional meeting, that if a small state with only a few members doesn't want to have a state meeting, it is not compelled to do so. The College, however, hopes that there will be enough interest manifested for some type of regional get-together once a year. Dr. Dowden did not think it appropriate for the College to dictate specific policy, but each Governor should be guided by what the majority of his members desire. In Kentucky, the members during the war and up to the present time had been joining with the large multi-state meetings for the Midwest region embodying Illinois, Indiana, Iowa, Michigan and Wisconsin, but very few of the Kentucky members had attended, whereas when Kentucky holds its own state meeting, ninety-five per cent of the members attend, which obviously is much to be preferred.

Dr. Joseph D. McCarthy, Governor for Nebraska, still advocated some expression of policy as to what these meetings shall be for and the form in which they shall be conducted. He asked whether the Governors are trying to put on minor annual meetings or are trying to accomplish other work within their individual states. He referred to the very large population of the College included in the Midwest Regional Meeting and intimated that the purpose of these large meetings, obviously, will be much different from the small, more personalized state meeting.

Dr. Walter L. Palmer, Governor for Northern Illinois, stated that when organizing his last meeting, he had consulted the Governors in the neighboring states to determine whether or not they, without obligation of any sort, wished to join in the large regional meeting at Chicago, and all of them voted to do so, whether wisely or unwisely. He stated further that he had called a meeting of all of the Governors concerned for a conference the day following this meeting of the Board of Governors to discuss again the question of whether the policy of joining together on this regional meeting shall be continued. He intimated that while it might be definitely desirable in Nebraska to have the restricted state meeting for the purposes previously suggested by Dr. McCarthy, it might not be feasible in a large populated area like Northern Illinois where the members are, to some extent, reasonably well known to one another. He pointed out that Chicago, for instance, is divided into four different medical school groups, a number of hospital staffs, with one society, the Chicago Society of Internal Medicine, to which most of the College Fellows in the area belong, and this society

conducts monthly meetings which provide an opportunity for the members to become acquainted. Dr. Palmer further felt that the type of multi-state regional meeting held in his area in no sense competes with the Annual Session because it is quite different in character. The local regional meeting program consists of fifteen-minute presentations largely by local, younger men. He expressed the opinion that the demands on the Annual Session program, including clinics, panel discussions, morning lectures, etc., are so great that a regional meeting program could in no sense compete.

Dr. R. R. Snowden, Governor for Western Pennsylvania, reported a Regional Meeting for that district had been held on September 11, 1946, during a postgraduate course in internal medicine conducted on the College program. During the war, Western Pennsylvania had joined up with Ohio and West Virginia in holding combined regional meetings which were not too well attended. Local Fellows had found the more personal, local meeting more stimulating and beneficial, with the result that Western Pennsylvania has been gratified to return to the purely local type of meeting where interests are common, where acquaintanceships are renewed, where a great deal of enthusiasm in the College is aroused and where younger men, interested in the College, may be invited as guests.

Chairman Dowden said that the deliberations and discussions of the Governors would be referred to the Board of Regents to see if that Board wishes to express any opinion or policy with regard to regional meetings.

Dr. George H. Lathrope, by resolution, was re-appointed a member of the Committee on Credentials from the Board of Governors for a three-year term, expiring 1950.

Chairman Dowden opened the meeting to a general discussion of policy with regard to the future of the College, character of the meetings, etc.

Dr. Lathrope stated that the question of increasing membership in the College is becoming acute. With continued growth, there is likely to develop difficulty in finding cities with adequate facilities to accommodate our present type of Annual Meeting. He suggested an amendment should be made to the By-Laws requiring that a candidate shall be thirty-five years of age before election to Associateship. He explained that while this appears radical, his experience on the Survey Committee of the College a year ago convinced him that there is a gradually sinking importance of the College as compared with the gradually rising importance, in the eyes of the young doctors, of the American Board. He cited a case where a Fellow recommended a young man for Fellowship recently wherein the recommendation referred only to the fact that he had passed his American Board examinations, and, therefore, is now "perfectly eligible" for Fellowship in the College. He emphasized, of course, that this is not what the rules and regulations of the College provide.

Dr. Burgess rose in support of Dr. Lathrope's point of view, to point out that if the age limit for entering Fellowship is thirty-eight or more, that would automatically make the age limit for Associateship as thirty-five, which, in his opinion, would be desirable. Dr. Burgess cited a recent instance which occurred at a meeting of the American Board of Internal Medicine in which the members felt that that organization, which is a creation of this College and has been made strong by the College requiring certification as one of its prerequisites, has now become almost too strong in position. Some members of the Board of Internal Medicine would agree that, in the minds of the young internists, too preponderant importance is given to the Board. He felt that Fellowship should be made a greater honor, more desirable and more selective. The College would advance in this direction, he thought, by adopting some general regulation as suggested by Dr. Lathrope; that certification should be required early, as a basis on which to build for qualification for Fellowship in the College. Certification, he said, should be a starter, showing that a man is qualified to be a specialist in internal medicine, but Fellowship in the College should show that he has fully qualified and has become a distinguished specialist.

Dr. E. V. Allen took the opposite point of view and expressed the belief that the purpose of the College should not be to recognize training, merit and experience. He felt that if the College has a function, it should be in the encouragement of attainment and education among younger men. He would be very reluctant, he said, to see the College become a group of middle-aged and older men who have achieved some prominence or eminence, a sort of old man's club, its chief function being to put its stamp of approval on a stage of respectability and merit. He felt it should be emphasized that the function of the College is that of education, that membership should not serve as a reward for attainment but as encouragement for attainment, encouragement for young men to strive for the things for which the College stands—scholarship, personal relations between the doctor and his patients and his associates. With regard to the American Board of Internal Medicine, Dr. Allen felt that there is no need for fear about its increasing importance since its function is only that of setting its stamp of approval on the training of an individual.

Dr. Edgar Hull likewise expressed opposition to any age limit for membership in the College, but suggested the possibility of lengthening the period allowable for Associateship in the College, thus not denying younger men the stimulation of junior membership in the College.

Dr. Cason said he would like to demonstrate democracy in action. He referred to at least two professors in medical schools who are under thirty years of age; while exceptions might be made for such men, it must be admitted that youth has brains. He stated that much of the fault in the increasing membership of the College is that of the Governors—that too many Governors endorse candidates whom they know are inadequately qualified. Too many candidates are “accommodated” when a careful analysis would show that their credentials are not up to the standards the College should expect. He cited cases of candidates for Associateship coming up at the age of forty-eight and fifty, men who had never previously thought of entering the College and who are definitely borderline cases. He thought Governors too often endorse ill-qualified candidates because they fear criticism of other Fellows. He referred to an early Convocation address made before the College when the speaker talked about autocracy and said that when the College grows too big, it would lose its importance and influence. Dr. Cason bespoke a plan which would become more selective but not be limited by age.

Dr. Allen, at this point, emphasized the fact that the Credentials Committee has the opportunity and the authority to determine the size of the College because it, in the final analysis, selects those who are elected.

Dr. Palmer expressed the opinion that the basic aspect of the problem, as previously touched upon by Dr. Hull, lies in the changing nature of the practice of medicine; that the general practitioner is doomed to extinction; that the specialist is going to have more and more his day. He emphasized the importance of seeing that the general practitioners of the future are well and thoroughly trained, and he asked whether The American College of Physicians is to consist only of the elite of that group and what shall be its criterion.

Dr. Snowden discussed a growing trend in some regions of institutions requiring staff members not only to be certified by the American Board of Internal Medicine, but also Fellows of The American College of Physicians. He thought that probably explains the reason why some internists now fifty or more years of age, faced with this problem suddenly, start attempting to qualify for Fellowship in the College. He thought it acceptable that certification be required but was inclined to suggest that Governors of the College discourage institutions, both teaching and hospital, from requiring Fellowship in the College as a prerequisite for staff membership. He felt that Fellowship in the College should be more than a stamp of approval that may be required by some hospital or teaching institution.

Dr. Burgess said it is the unanimous opinion of members of the American Board of Internal Medicine that a hospital which requires certification for promotion on a staff is not living up to its own responsibilities; the hospital should be able to judge its own members for advancement and should not put any such problem up to any board anywhere. Dr. Burgess then, referring to previous discussions by Dr. Allen, decried any attempt to "pass the buck" from the Board of Governors to the Credentials Committee in regard to the selection of candidates. He felt it the function of the Board of Governors to make the most careful selection of candidates before individual Governors shall endorse them and send their credentials to the Committee. A Governor has a greater opportunity to investigate a candidate in his own state and among his own Fellows than has a small Credentials Committee acting for the country at large. He urged Governors to be thorough and specific in their recommendations to the Credentials Committee.

Chairman Dowden asked the Board, and particularly Dr. Lathrope, if any particular action were desired—some resolution, the appointment of a committee to study the problem further and report back later.

Dr. Lathrope thought that no particular resolution was required because the purpose of the original discussion was to air the situation generally and to obtain the opinions of the individual members of the Board. He felt the discussion had been exceedingly helpful and productive of much good not only among the Governors but among the members of the Credentials Committee.

CHAIRMAN DOWDEN: "The time has come when the Board must consider the election of a new Chairman. I should like to express my appreciation of your courtesy and of your support and patience. I have appreciated your unfailing courtesy, your support and your attendance at our meetings."

In the regular manner prescribed by the By-Laws, Dr. Walter L. Palmer was elected Chairman of the Board of Governors for a three-year term, expiring in 1950. Dr. Palmer responded, expressing his deep appreciation of the honor and assuring the Board of his greatest efforts to uphold the duties of the office and to maintain the splendid record set by the retiring Chairman, Dr. Dowden.

Dr. Allen, on behalf of the Board of Governors, rose to express to the retiring Chairman "our gratitude and our true affection for the Chairman we have had for the past few years." (All members of the Board arose and applauded.)

Dr. Allen introduced the recommendation that the meeting time of the Board of Governors should be carefully studied with a view to arranging a schedule at the next Annual Session by which the meetings would not conflict with the scientific program and by which the Governors might have more adequate time for their deliberations. He suggested the possibility of meeting during the forenoon of the first day or some other acceptable arrangement.

It was pointed out that the Secretary, Mr. Loveland, is also Secretary of the Board of Regents, the general business manager of the Annual Session, and that the schedule heretofore has been worked out in such a manner as to enable him to perform his duties as required under the By-Laws.

Dr. Yater suggested the possibility of the Board having its first meeting on Tuesday evening when there is no other conflicting event. Obviously, the Board of Governors cannot meet at the same time as the Board of Regents because not only is Mr. Loveland the Secretary of each Board, but the Chairman of the Board of Governors is also a member of the Board of Regents.

On motion by Dr. Allen, seconded by Dr. Yater and regularly carried, it was resolved that the Chairman and the Executive Secretary be requested to arrange a better meeting time for the Board of Governors to allow for longer and adequate discussions.

Adjournment—3 p.m.

Attest: E. R. LOVELAND

*Secretary*

*OBITUARIES*

## DR. F. WARNER BISHOP

Dr. F. Warner Bishop, of New York City, died in St. Luke's Hospital on March 23, 1947.

Dr. Bishop was born in Brooklyn, N. Y., on April 18, 1887. He received his academic and medical training at Columbia University, from which he received the B.S. and M.D. degrees in 1910 and 1912. Most of his medical life was devoted to St. Luke's Hospital where, at the time of his death, he was an Attending Physician. From 1936 to 1938 he served as President of St. Luke's Medical Board. He at one time held appointments as Instructor in Physiology and in Clinical Medicine in Columbia University.

Dr. Bishop was a member of the Medical Societies of the State and County of New York; of the New York Academy of Medicine; the New York Clinical Society, of which he was formerly President; and of the American Heart Association. He had been a Fellow of the American College of Physicians since 1937.

Dr. Bishop was a very highly respected member of the medical profession and a skilled physician.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

## DR. JOHN LEONARD KANTOR

Dr. John Leonard Kantor, a leading gastro-enterologist of New York City, died at Mt. Sinai Hospital, June 25, 1947.

Dr. Kantor was born in Moscow, Russia, on April 12, 1890, and came to this country the following fall. He attended Columbia University, receiving the degree of Bachelor of Arts in 1908, and the M.D. and Ph.D. degrees four years later. He then served a three-year internship in the Mt. Sinai Hospital, and entered the Army Medical Corps as a specialist in gastro-enterology during the First World War.

Dr. Kantor became associated with the faculty of the Columbia University College of Physicians and Surgeons in 1916 and rose to the position of Associate Clinical Professor of Medicine. From 1919 to 1935 he was on the staff of the Vanderbilt Clinic, where he served as Chief of the Clinic of Gastrointestinal Diseases. He also served as Associate Roentgenologist at the Montefiore Hospital for Chronic Diseases, as Gastro-enterologist at the Beth David Hospital, and as Consultant in gastrointestinal diseases to the Will Rogers Memorial Hospital, Saranac Lake, N. Y., the National Jewish Hospital, Denver, Colo., and the Sharon (Conn.) Hospital.

During World War II, Dr. Kantor saw active service in New Guinea as Chief of the 49th General Hospital.

Dr. Kantor was a member of the New York Academy of Medicine and of the New York Gastro-enterological Association, of which he was a former President. He was also a member of the American Medical Association, the American Roentgen Ray Society, the Association of Military Surgeons of the United States, the Medical Societies of the State and County of New York, and of Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha, Phi Delta Epsilon. A Diplomate of the American Board of Internal Medicine, Dr. Kantor was elected to Fellowship in the American College of Physicians in 1938.

His premature death means a real loss to the medical profession of New York City.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. WASHINGTON MERSCHER

Dr. Washington Merscher of Clifton Springs, N. Y., died suddenly on June 15, 1947. Dr. Merscher had just become a Fellow of the College, by direct election, on April 27, 1947.

Dr. Merscher was born December 9, 1888, at Philadelphia, Pa. He was graduated from the University of Pennsylvania School of Medicine in 1910. He interned in the Germantown Dispensary and Hospital and entered practice in Philadelphia. During his period of practice in that city, he served on the Medical Staffs of the Roxboro Memorial Hospital and the Germantown Dispensary and Hospital. From 1934 to 1937 he held appointments in the Temple University School of Medicine as Instructor in Medicine. In 1937, following an illness, he removed to Watkins Glen, N. Y., where he became Chief of the Medical Service of the Glen Springs Sanatorium. In 1943 he joined the staff of The Clifton Springs Sanatorium and Clinic as an internist.

Dr. Merscher was a member of the Ontario and the Schuyler County Medical Societies, New York; of the Medical Society of the State of Pennsylvania; and was a Fellow of the American Medical Association.

Dr. Merscher was recently the head of the Gastro-enterological Section at The Clifton Springs Sanatorium.

He was regarded by his associates as a very capable internist and was especially beloved by his patients because of his kindly manner and interest in them.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,  
Governor for Western New York

## DR. WILLIAM TIMOTHY O'HALLORAN

Dr. William T. O'Halloran of Newtonville, Mass., died at his home on May 21, 1947, following a coronary thrombosis. At the time of his death he was Chief of the Sixth Medical Service of the Boston City Hospital and Assistant Professor of Medicine at Boston University School of Medicine.

Dr. O'Halloran graduated from Tufts College Medical School and joined the staff of the Boston City Hospital, where he advanced over the years from house officer to Chief of the youngest of the Medical Services of the hospital.

Dr. O'Halloran was a member of the Newton Medical Club, American Heart Association, New England Heart Association, Massachusetts Medical Society; was a Fellow of the American Medical Association and, since 1941, of the American College of Physicians. He was considered a skillful physician and loyal friend by his colleagues, and he commanded the respect of all who served with him.

CHESTER S. KEEFER, M.D., F.A.C.P.,  
Governor for Massachusetts

## DR. JOHN WILLIAM PRESTON

John William Preston, M.D., F.A.C.P., Roanoke, Va., died January 1, 1947, age 79 years. He graduated from the College of Physicians and Surgeons, Baltimore, in 1893. He pursued postgraduate work at the University of Pennsylvania, Harvard Medical School, the Johns Hopkins Hospital and at the University of London, in subsequent years. He became a member of the American Congress on Internal Medicine in 1921 and a Fellow of The American College of Physicians in 1922. He had been in the practice of internal medicine at Roanoke for many years. He was a Diplomat of the American Board of Internal Medicine and since 1917 had been the Secretary-Treasurer of the Virginia State Board of Medical Examiners. During World War II, he was Chairman of the Medical Advisory Board for Roanoke and a member of the Army Induction Board.

## DR. HOWARD GUSTAV SCHLEITER

Dr. Howard Gustav Schleiter, F.A.C.P., of Pittsburgh, Pa., widely known cardiologist, died on February 5, 1947, after a brief illness. Born in Pittsburgh, May 27, 1880, he received his A.B. degree from Harvard College and M.D. degree from the University of Pennsylvania. After postgraduate work at Mt. Vernon Hospital and the University College Hospital, London, England, he devoted more and more of his time and energy to diseases of the cardiovascular system, in which field his knowledge, experience, and sound judgment were widely recognized.

Dr. Schleiter was for many years Visiting Physician to the St. Francis Hospital, and Associate Professor of Medicine in the School of Medicine, University of Pittsburgh. At the time of his death he was Chief of the Cardiological Service of the Allegheny General Hospital, and of the Pittsburgh Diagnostic Clinic. Dr. Schleiter was a Diplomate of the American Board of Internal Medicine.

He was a member and former President, Pittsburgh Academy of Medicine; member, Allegheny County Medical Society, Pennsylvania State Medical Society, American Medical Association, American Clinical and Climatological Society, and the American Rheumatism Society; a Fellow of the American College of Physicians since 1930.

Dr. Schleiter was a man of wide cultural attainments. He was particularly interested in music and was himself a pianist of unusual ability. Widely traveled, with his broad education and intense interest in all the arts, a fluent and witty conversationalist, he was at all times an interesting and stimulating companion. His untimely death takes from us an able physician and an inspiring friend.

R. R. SNOWDEN, M.D., F.A.C.P.,  
Governor for Western Pennsylvania

#### DR. WILLIAM F. SCHROEDER

Dr. William F. Schroeder, F.A.C.P., of Rock Island, Ill., died on June 10, 1947.

Dr. Schroeder was born in Rock Island on September 24, 1885. He attended the University of Illinois, by which he was awarded the Degree of Bachelor of Arts, in 1909. During World War I, he served in the U. S. Army, and achieved the rank of Captain of Infantry. Subsequently Dr. Schroeder attended the University of Minnesota. The degrees of Bachelor of Science (1922) and Doctor of Medicine (1926) were conferred upon him by that institution.

Dr. Schroeder served as a member of the medical staffs of the Lutheran and Moline Public Hospitals, Moline, Ill.; of St. Luke's Hospital, Davenport, Iowa; and as former Chief of Staff of St. Anthony's Hospital, in Rock Island.

Dr. Schroeder was a member of the Illinois and Iowa State Medical Societies, and a past President of the Rock Island County Medical Society. He was a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1932.

Dr. Schroeder found legitimate pride in attempting to solve many problems that came to his patients, whether medical, social or economic. He was a kindly, understanding companion to all. His unfaltering loyalty to his patients and to the best interests in his profession will long be remembered.

HARRY W. SHUMAN, M.D., F.A.C.P.



## DR. GEORGE MUNRO GOODWIN

Dr. George Munro Goodwin, F.A.C.P., of New York City, died July 12, 1947, after a brief illness in St. Luke's Hospital. He was Director of Medicine in St. Luke's Hospital and Professor of Clinical Medicine in the College of Physicians and Surgeons of Columbia University.

Dr. Goodwin was born in Brooklyn, October 24, 1887, received his medical degree from Columbia University College of Physicians and Surgeons in 1911, and interned in St. Luke's Hospital, with which institution he has been associated for the past 36 years, having advanced through various grades until he was made Director of Medicine in 1945. He was also Consultant in Medicine at the New York Orthopedic Hospital.

In the early years of his practice, Dr. Goodwin was very closely associated with the late Dr. Samuel W. Lambert and with Dr. Henry W. Patterson. He was formerly President of the Medical Board of St. Luke's Hospital, a member of many medical societies, a Diplomat of the American Board of Internal Medicine and had been a Fellow of The American College of Physicians since 1937.

Dr. Goodwin was a specialist in internal medicine and perhaps will be remembered best as a teacher of medicine. His untimely death is a very distinct loss to the medical profession.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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## THE MECHANISM OF RECOVERY IN ACUTE BACTERIAL PNEUMONIA \*

By W. BARRY WOOD, JR., F.A.C.P., *St. Louis, Missouri*

ALTHOUGH the treatment of acute bacterial pneumonia has been revolutionized in recent years by the advent of chemotherapy, the exact mechanism of recovery is not known. Pertinent to the problem are the following basic facts:

1. Most of the bacteria that cause the more common forms of acute pneumonia are encapsulated (pneumococcus, beta hemolytic streptococcus, Friedländer's bacillus, influenza bacillus, staphylococcus), and the presence of the capsules renders the organisms resistant to phagocytosis.<sup>1</sup> According to present concepts of immunology, fully encapsulated microorganisms can be phagocytosed only in the presence of suitable opsonins.<sup>2</sup>

2. Sulfonamide drugs that are highly effective in the treatment of pneumococcal pneumonia act only as bacteriostatic agents in the concentrations attained by systemic therapy.<sup>3</sup> Likewise, penicillin, in the relatively low concentrations needed to cure pneumococcal pneumonia,<sup>4, 5</sup> will not kill pneumococci consistently in the presence of tissue.<sup>6</sup> † Thus the final destruction of the invading bacteria appears to depend upon the defenses of the host, and particularly upon phagocytosis.<sup>7</sup>

3. Intensive chemotherapy usually brings about recovery long before type specific antibody can be detected in the patient's blood serum.<sup>8, 9</sup> Histologic studies in experimental animals have demonstrated that phagocytosis takes place in the lung in the absence of both circulating and local antibody.<sup>10</sup>

From the above facts it is apparent that the most important question that remains unanswered concerns the mechanism whereby phagocytes in the lung destroy fully encapsulated bacteria in the absence of immune bodies.

\* Presented before the Twenty-Eighth Annual Session of the American College of Physicians, Chicago, Illinois, April 29, 1947.

From the Department of Medicine and the Oscar Johnson Institute for Medical Research, Washington University School of Medicine, St. Louis, Missouri. The experimental studies were supported by a grant from the Commonwealth Fund.

† When injected locally in sufficient concentration, penicillin is bactericidal.<sup>6</sup>

*A. Pathogenesis of Pulmonary Lesion.* During the past decade, a clearer understanding of the pathogenesis of acute bacterial pneumonia has been gained by histological analysis of experimental infections in laboratory animals.<sup>11-15</sup> The previously accepted concept that pneumococci causing pneumonia spread through the lung via the lymphatics<sup>16-18</sup> has been conclusively refuted,<sup>14</sup> and evidence has been presented from several laboratories that the invading organisms are carried through the lungs by infected edema fluid at the outer margin of the lesion.<sup>11, 12, 13</sup> Careful histological studies in both pneumococcal and Friedländer's bacillus pneumonia, indicate that the bacteria enter new alveoli through the pores of Cohn and via the bronchial tree.<sup>13, 15</sup> Robertson and Hamburger<sup>19</sup> have shown that interlobar spread in experimental pneumococcal pneumonia results from the passage of heavily infected edema fluid into the main bronchi of previously uninfected lobes.

Although the principal mechanism of spread of pneumonia through the lungs does not involve the lymphatics, it is clear that many of the invading organisms enter lymphatic channels and are thus carried to regional lymph nodes.<sup>20-22</sup> Bacteria that get by the lymph node barriers eventually reach the thoracic duct and are poured into the blood stream,<sup>22, 23</sup> causing bacteremia.

The pathogenesis of pleurisy and empyema is not clearly understood. The fact that the lymphatics at the periphery of the lung drain outward toward the pleura<sup>24</sup> suggests that the bacteria may enter the pleural space either via the lymphatics or by passing directly through the pleura from the underlying infected alveoli.

Only the outermost zone of the spreading pneumonic lesion is characterized by the presence of edema fluid. In the more central, older portions of the lesion the alveoli become filled with leukocytic exudate, and the edema fluid disappears.<sup>13, 15</sup> As the alveolar exudate becomes more concentrated, phagocytosis of the bacteria occurs, and frequently no bacteria can be found in the most central portions of the lesion. In such areas signs of resolution are present when the pneumonia is still advancing at the periphery.<sup>13, 15</sup> These histological features of the spreading pneumonic lesion as observed in experimental animals have also been described in the lungs of patients dying of pneumococcal pneumonia.<sup>25</sup>

Of particular interest is the fact that pneumococci are phagocytosed and destroyed in the lungs of both animals and patients dying of the disease.<sup>10, 13, 25</sup> Since the pulmonary lesions contain large amounts of specific soluble substance, which combines with and neutralizes the opsonizing action of specific antibody,<sup>26</sup> and since under such conditions no free antibody can be demonstrated either in the blood serum or in the lungs,<sup>9</sup> it appears that leukocytes in the lung can phagocyte and destroy pneumococci in the absence of immune bodies, even in untreated fatal pneumonia.

*B. Effect of Chemotherapy upon Lesion.* The effect of chemotherapeutic agents upon the pulmonary lesions of both experimental pneumococcal and Friedländer's bacillus pneumonia has been studied in white rats.<sup>6, 15</sup>

Within a few hours after the start of treatment the bacteria in the outer edema zone of the lesions exhibit morphological changes indicative of bacteriostasis. Soon after the organisms cease multiplying, the edema zone disappears from the edge of the lesions, and phagocytic cells accumulate in the infected alveoli. Within 24 hours phagocytosis is noted even in the periphery of the now stationary lesions, and, in time, all of the bacteria are engulfed and destroyed by the phagocytic cells. After three to four days resolution of the pneumonic lesion becomes evident, with only a few large macrophages remaining in the previously infected alveoli. Repeated examinations have failed to reveal either circulating or local antibody at the time that the phagocytic reaction is most prominent in the lungs.<sup>9, 27</sup> Thus, direct histological studies of the recovery process during chemotherapy have shown that most of the bacteria in the lung are destroyed by phagocytic cells, and that this phagocytic reaction occurs in the absence of opsonins.

*C. Non-Antibody Mechanism of Phagocytosis.* When pneumococci are incubated with leukocytes in a fluid medium devoid of antibody, no phagocytosis takes place.<sup>28</sup> The leukocytes can be seen to push aside the organisms with which they come in contact during their migration through the fluid medium. If, however, mixtures of leukocytes and pneumococci in the same fluid medium are incubated upon various body tissues or upon rough inert materials such as filter paper, phagocytosis results. The manner in which the leukocytes successfully attack the encapsulated organisms on such surfaces is best shown by observing the process directly under the microscope in thin sections of formalin-fixed lung. In such preparations, the leukocytes can be seen to phagocyte the bacteria by trapping them against the tissue surfaces of the alveolar walls. Bacteria thus pinned against the tissue surfaces cannot escape phagocytosis.<sup>28</sup> Fully encapsulated strains of Friedländer's bacillus, pneumococcus type III, beta hemolytic streptococcus and staphylococcus have all been shown to be susceptible to surface phagocytosis.<sup>29</sup>

When sufficient numbers of leukocytes are present in the mixtures, the encapsulated bacteria are phagocytosed not only by being trapped against tissue surfaces, but also by being caught between the surfaces of the phagocytic cells themselves.<sup>30</sup> The intercellular surface phagocytosis can be clearly demonstrated merely by concentrating the phagocyte-bacteria mixtures through centrifugation. When such concentrated mixtures are incubated, even in a test tube, marked phagocytosis results. Once taken into the cytoplasm of the phagocytes, the bacteria are promptly killed.<sup>28, 31</sup> Through these two forms of surface phagocytosis leukocytes may bring about destruction of encapsulated bacteria in the lung, in the complete absence of opsonins.\*

*D. Relation of Surface Phagocytosis to Recovery.* The first stage of any acute inflammatory reaction is characterized by the outpouring of edema fluid into the inflamed area, and is promptly followed by a rapid accumulation of leukocytes. This familiar sequence of events occurs in acute bacterial

\* Photomicrographs of the phagocytic phenomena described in this report have already been published.<sup>28, 30, 31</sup>

pneumonia, and during effective chemotherapy all of the invaded alveoli and bronchi eventually become packed with leukocytes.<sup>6</sup> The concentration of phagocytic cells in the consolidated areas of the lung makes it virtually impossible for bacteria to escape surface phagocytosis. Those organisms that are not phagocyted by being trapped against the tissue surfaces of the alveoli and bronchi are eventually pinned between the surfaces of two or more of the crowded leukocytes and are engulfed by the intercellular mechanism. Thus, the bacteriostatic action of the chemotherapeutic drug controls the spread of the lesion, and the leukocytes, through surface phagocytosis, destroy the bacteria that remain in the lung.

Since all of the invading organisms in acute bacterial pneumonia do not remain in the lung, those that enter the lymphatics and blood stream must eventually be accounted for in the process of recovery. There is indirect evidence that most of the organisms that escape from the lung are destroyed in the lymph nodes<sup>32</sup> and in such organs as the spleen, liver, and bone marrow.<sup>33</sup> The manner in which encapsulated bacteria are destroyed in these extra-pulmonary sites, in the absence of circulating immune bodies, is at present under investigation. It seems not unlikely that surface phagocytosis may operate in the sinusoids of the lymph nodes, liver, spleen, and bone marrow as well as in the lung.

The failure of phagocytic cells during systemic chemotherapy to sterilize areas of abscess formation, both within and outside the lung, deserves special comment. It is well known that patients with empyema and other suppurative complications of pneumonia are rarely cured by systemic chemotherapy alone.<sup>34, 35</sup> Studies of experimental Friedländer's bacillus pneumonia in rats have shown that complicating lung abscesses, that frequently develop during treatment, cannot be sterilized by intensive sulfonamide therapy.<sup>31</sup> The failure of leukocytes to rid abscesses of all bacteria would appear to be due to at least two factors. First, the absence of the normal tissue structures in abscessed areas deprives the leukocytes of the surfaces upon which they normally operate in intact tissue. Secondly, many of the leukocytes, particularly in the center of a large abscess, are either non-viable or so sluggish that they cannot phagocyte bacteria. Leukocytes deprived of oxygen quickly become non-motile and lose their phagocytic properties.<sup>36</sup> Since the only source of oxygen for leukocytes in an abscess is the intact capillaries at the periphery of the lesion, it is not surprising that the phagocytes in the central mass of pus fail to sterilize the lesion. To cure by chemotherapy such purulent complications as pneumococcal empyema, it is necessary, therefore, to inject large enough amounts of penicillin locally to obtain a bactericidal effect.<sup>34</sup>

It is not implied by the present analysis that antibody plays no rôle in the mechanism of recovery in pneumonia. It is known that antibody, when present in sufficient quantity, will agglutinate the bacteria in the outer edema zone of pneumonic lesions and will thus stop the spread of the infection.<sup>12</sup> Likewise, lesser amounts of antibody opsonize encapsulated bacteria and

greatly facilitate phagocytosis.<sup>13, 28</sup> Natural antibodies, however, are usually neutralized in the early stage of the acute infection,<sup>37</sup> and the production of acquired antibody by the host is a relatively slow process,<sup>38</sup> as is evidenced by the fact that complete recovery frequently takes place hours, and even days, before antibody can be demonstrated either at the site of the pneumonia or in the circulating blood.<sup>9, 27</sup> Surface phagocytosis, on the other hand, serves as an immediate defense reaction of the host against the invading bacteria.<sup>28, 30, 31, 39</sup> This more prompt form of phagocytic reaction which operates in the absence of antibody appears to account for the rapid destruction of bacteria that occurs in the lung as the result of effective chemotherapy.

### SUMMARY

Evidence is presented that, following adequate chemotherapy, prompt recovery from acute bacterial pneumonia depends in large measure upon the bactericidal effect of surface phagocytosis, a defense mechanism of the host that operates in the absence of immune bodies.

### BIBLIOGRAPHY

1. DUBOS, R. J.: The bacterial cell, 1945, Harvard University Press, Cambridge, p. 205.
2. ZINSSER, H., ENDERS, J. F., and FOTHERGILL, L.: Immunity, principles and application in medicine and public health, 1939, MacMillan Co., New York, p. 18.
3. FINLAND, M., SPRING, W. C., JR., and LOWELL, F. C.: Studies on the action of sulfapyridine on pneumococci, *Jr. Clin. Invest.*, 1940, xix, 163.
4. TILLET, W. S., CAMBIER, M. J., and McCORMACK, J. E.: The treatment of lobar pneumonia and pneumococcal empyema with penicillin, *Bull. N. Y. Acad. Med.*, 1944, xx, 142.
5. FINLAND, M., MEADS, M., and ORY, E. M.: Oral penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 315.
6. HEILMAN, D. H., and HERRELL, W. E.: Comparative antibacterial activity of penicillin and gramicidin: tissue culture studies, *Proc. Staff Meet. Mayo Clin.*, 1942, xvii, 321.
7. WOOD, W. B., JR., and IRONS, E. N.: Studies on the mechanism of recovery in pneumococcal pneumonia, *Jr. Exper. Med.*, 1946, lxxxiv, 365.
8. WOOD, W. B., JR., and LONG, P. H.: Observations upon the experimental and clinical use of sulfapyridine, *Ann. Int. Med.*, 1939, xiii, 612.
9. FINLAND, M., SPRING, W. C., and LOWELL, F. C.: Immunological studies on patients with pneumococcal pneumonia treated with sulfapyridine, *Jr. Clin. Invest.*, 1940, xix, 179.
10. WOOD, W. B., JR., McLEOD, C., and IRONS, E. N.: Studies on the mechanism of recovery in pneumococcal pneumonia, *Jr. Exper. Med.*, 1946, lxxxiv, 377.
11. ROBERTSON, O. H.: Some recent studies of experimental lobar pneumonia: pathogenesis, recovery and immunity, *Jr. Am. Med. Assoc.*, 1938, cxi, 1432.
12. GUNN, F. D., and NUNGESTER, W. J.: Pathogenesis and histopathology of experimental pneumonia in rats, *Arch. Path.*, 1936, xxi, 813.
13. WOOD, W. B., JR.: Studies on the mechanism of recovery in pneumococcal pneumonia, *Jr. Exper. Med.*, 1941, lxxiii, 201.
14. LOOSLI, C. G.: The pathogenesis and pathology of experimental Type I pneumococcal pneumonia in the monkey, *Jr. Exper. Med.*, 1942, lxxvi, 79.
15. SALE, L., JR., and WOOD, W. B., JR.: Studies on the mechanism of recovery in pneumonia due to Friedländer's bacillus. I. The pathogenesis of experimental Friedländer's bacillus pneumonia. In press.

16. BLACK, F. G., and CECIL, R. L.: Studies on experimental pneumonia, Jr. Exper. Med., 1920, xxxi, 445.
17. PERMAR, H. H.: The pathogenesis of experimental pneumonia in the rabbit, Jr. Med. Res., 1923, xli, 1.
18. BRANCH, A., and STILLMAN, E. G.: Pathology of experimental pneumococcus pneumonia in mice, Jr. Exper. Med., 1924, xl, 743.
19. ROBERTSON, O. H., and HAMBURGER, M.: Studies on the pathogenesis of experimental pneumococcus pneumonia in the dog, Jr. Exper. Med., 1940, lxxii, 275.
20. ROBERTSON, O. H.: Phagocytosis of foreign material in the lung, Physiol. Rev., 1941, xxi, 112.
21. YOUNG, G. A., ZELBE, M. R., and LINCOLN, R. E.: Respiratory pathogenicity of *Bacillus anthracis* spores, Jr. Infect. Dis., 1946, lxxix, 233.
22. LOOSLI, C. G.: Personal communication.
23. SCHULZ, R. Z., WARREN, M. F., and DRINKER, C. L.: The passage of rabbit virulent Type III pneumococci from the respiratory tract of rabbits into the lymphatics and blood, Jr. Exper. Med., 1938, lxxviii, 251.
24. MILLER, W. S.: The lung, 1937, Charles C. Thomas, Baltimore, p. 108.
25. LOESCHCKE, H.: Untersuchungen über die Kruppöse Pneumonie, Beitr. z. path. Anat. u. z. allg. Path., 1931, lxxxvi, 201.
26. NYE, R. N., and HARRIS, A. H.: Viable pneumococci and pneumococcic specific soluble substances in the lungs from cases of lobar pneumonia, Am. Jr. Path., 1937, xiii, 749.
27. SALE, L., JR., SMITH, M. R., and WOOD, W. B., JR.: Studies on the mechanism of recovery in pneumonia due to Friedländer's bacillus. II. The effect of sulfonamide chemotherapy upon the pulmonary lesion of experimental Friedländer's bacillus pneumonia. In press.
28. WOOD, W. B., JR., SMITH, M. R., and WATSON, B.: Studies on the mechanism of recovery in pneumococcal pneumonia, Jr. Exper. Med., 1946, lxxxiv, 387.
29. WOOD, W. B., JR., and SMITH, M. R.: To be published.
30. WOOD, W. B., JR., and SMITH, M. R.: Intercellular surface phagocytosis. In press.
31. SMITH, M. R., and WOOD, W. B., JR.: Studies on the mechanism of recovery in pneumonia due to Friedländer's bacillus. III. The rôle of "surface phagocytosis" in the destruction of the microorganisms in the lung. In press.
32. DRINKER, C. K., and YOFFE, J. M.: Lymphatics, lymph and lymphoid tissue, 1941, Harvard University Press, Cambridge, p. 170.
33. BEESON, P. B., BRANNON, E. S., and WARREN, J. V.: Observations on the sites of removal of bacteria from the blood in patients with bacterial endocarditis, Jr. Exper. Med., 1945, lxxxix, 9.
34. TILLET, W. S., McCORMACK, J. E., and CAMBIER, M.: The use of penicillin in the local treatment of pneumococcal empyema, Jr. Clin. Invest., 1945, xxiv, 595.
35. KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., LOCKWOOD, J. S., and WOOD, W. B., JR.: Penicillin in the treatment of infections, Jr. Am. Med. Assoc., 1943, cxxii, 1217.
36. SMITH, M. R., and WOOD, W. B., JR.: Unpublished observations.
37. ROBERTSON, O. H., GRAESER, J. B., COGGESHALL, L. T., and HARRISON, M. A.: The relation of circulating antipneumococcal immune substances to the course of lobar pneumonia, Jr. Clin. Invest., 1934, xiii, 621.
38. CURNEN, E. C., and MACLEOD, C. M.: The effect of sulfapyridine upon the development of immunity to pneumococcus in rabbits, Jr. Exper. Med., 1942, lxxv, 77.
39. WOOD, W. B., JR., and SMITH, M. R.: Surface phagocytosis—its relation to the mechanism of recovery in pneumococcal pneumonia, Science, 1946, civ, 28.

# BAL IN THE TREATMENT OF TOXICITY FROM GOLD \*

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THE value of therapy with gold salts in rheumatoid arthritis has been recognized increasingly as a useful addition to the therapeutic program in this disease. Unfortunately, toxic effects of varying degrees of severity have hindered wider employment of chrysotherapy and have often forced its discontinuance upon the appearance of the early signs of toxicity. The many types of toxic reactions resulting from chrysotherapy in rheumatoid arthritis will not be enumerated here since this subject has been discussed elsewhere.<sup>1</sup>

There has been a long felt need for some agent to counteract the toxic effects of gold therapy. Although various measures have been tried in the past, none proved effective.

In view of the reported observations on the effectiveness of British Anti-Lewisite (BAL) in the systemic treatment of arsenic and mercury poisoning,<sup>2</sup> it appeared to us that study of the possible effectiveness of BAL in the treatment of toxic reactions from gold should be undertaken. We have had occasion to observe the effect of the administration of BAL in five cases of toxic complications resulting from the use of gold in the treatment of rheumatoid arthritis. The striking benefit which was noted in one of these cases and the seemingly beneficial effect in three others warrants this preliminary report.

BAL (2,3-dimercaptopropanol) is a compound developed in England during the last war by Peters, Stocken, and Thompson<sup>3</sup> as a decontaminating and neutralizing agent against the arsenical blister gas, Lewisite. For this reason this new compound was named British Anti-Lewisite and has been marketed under the trade name of BAL.

It has been suggested that the toxic effect of arsenicals results from interference with cellular metabolism, since the heavy metal combines with SH groups in the tissues. BAL is presumed to exert its beneficial effect because of its affinity for the arsenical, combining with it before the metallic arsenic combines with the tissues, or by removal of the arsenic from the tissues after it has already combined.<sup>4</sup> It has also been intimated that the toxic effect of other heavy metals may be the result of a similar biologic action.<sup>5</sup>

## CASE REPORTS

*Case 1.* Mrs. A. G., a white woman 38 years of age, was first seen on August 21, 1946, with rheumatoid arthritis of two months' duration, involving both knees and ankles. There was evidence of synovial swelling of the knees and ankles; the tonsils

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appeared to be infected. The sedimentation rate was accelerated to 24.5 mm. in 60 min. (Cutler method). Roentgenograms of both knees and the left ankle were normal.

In addition to systemic management and physiotherapy, treatment with aurothio-glucose (Solganol B Oleosum) was instituted as follows:

August 24, 1946	.010 gm.	Total .010 gm.
August 31, 1946	.020 gm.	Total .030 gm.
September 7, 1946	.020 gm.	Total .050 gm.
September 14, 1946	.020 gm.	Total .070 gm.
September 21, 1946	.030 gm.	Total .100 gm.
September 29, 1946	.030 gm.	Total .130 gm.
October 12, 1946	.030 gm.	Total .160 gm.
October 24, 1946	.040 gm.	Total .200 gm.
November 2, 1946	.040 gm.	Total .240 gm.

By September 28, the joint pains and swelling had completely subsided. The sedimentation rate had improved to 20 mm. in 60 min. (Cutler method). On October 24, 1946, tonsillectomy was performed with uneventful healing at the operative site. On November 6, 1946, minute areas of ulceration appeared on the lower lip. Further administration of gold was discontinued. Nevertheless, by November 30, 1946, the patient had developed a severe ulcerative stomatitis and cheilitis involving especially the mucous membranes of both lips and the angles of the mouth, as well as a marked papulo-vesicular eruption of the skin around the mouth. The lips were swollen and injected, and the ulceration was so extensive that opening the mouth or eating induced bleeding from the ulcerated surface. On November 30, 1946, treatment with BAL was started, .150 gm. being given intramuscularly four times daily for two days, and .150 gm. twice daily, thereafter. Because of the appearance of nausea, it was necessary to reduce the dose after the fourth day to .100 gm. twice daily. After eight days of such treatment, during which time a total of 2.6 gm. of BAL had been administered, the stomatitis and surrounding area of dermatitis had cleared completely.

This case demonstrated the striking and dramatic recovery from severe stomatitis resulting from the administration of a fairly soluble gold salt preparation. BAL was started 24 days following onset of the toxic stomatitis which was increasing in severity until administration of BAL was instituted. Within eight days, during which 2.6 gm. of BAL had been given, the stomatitis cleared entirely.

*Case 2.* Mr. E. R. H., a white man 61 years of age, was first seen on March 19, 1946, with rheumatoid arthritis of seven months' duration, associated with bronchiectasis, diagnosed by bronchoscopy four years previously. Examination revealed a thin, pallid man. The proximal interphalangeal and metacarpophalangeal joints and both wrists presented typical rheumatoid changes. The right ankle was swollen and both knees presented synovial and capsular thickening. There was limitation of motion of both shoulders. The sedimentation rate was accelerated to 23 mm. in 60 min. (Cutler method). Roentgenograms of the right ankle, hands, and wrists revealed characteristic rheumatoid decalcification of the bones, but no narrowing of the joint spaces. The film of the chest indicated increased peribronchial infiltration.

In addition to the usual systemic measures and physiotherapy, treatment with aurothioglycolanilide (Lauron) was started. He received .150 gm. of Lauron from March 20 to April 5, 1946; thereafter .200 gm. to .300 gm. weekly until September 9, 1946, at which time a total of 3.150 gm. of Lauron had been administered. On September 23, 1946, he reported a transitory stomatitis of the roof of the mouth. Further gold was withheld for one month. On August 25, 1946, and again on September 7, 1946, .200 gm. of Lauron was administered, making a total of 3.550 gm. On Sep-

tember 25, 1946, a small anal excoriation with pruritus appeared; further administration of gold was discontinued. The ulceration persisted despite local therapy and on October 25, 1946, the patient reported a mild conjunctivitis and a solitary ulcer of the mouth. At this time the joints were generally improved. On November 22, 1946, scaliness of both upper eyelids was noted, and on December 13, 1946, he complained of pruritus and a scaly dermatitis of the scrotum and left hand.

Administration of BAL was started on December 20, 1946, with a dosage of .150 gm. intramuscularly four times daily. He had received a total of .900 gm. in a period of two days when administration of the drug was discontinued because of local soreness at the sites of injection. By January 3, 1947, the anal ulceration had improved and the scrotal dermatitis had completely subsided, but the conjunctivitis and scaly dermatitis of the eyelids, and left hand were unchanged. BAL was again administered from January 3, 1947, to January 10, 1947, with a dosage of .150 gm. twice daily for an additional total of 2.4 gm., following which the residual dermatitis of the left hand, the conjunctivitis, and the anal ulceration had entirely cleared.

In this instance involvement of the skin and mucous membranes of the eyes, mouth, and arms resulting from the administration of a slowly absorbed gold salt preparation was neither extensive nor severe; however, it did not respond to local therapy. BAL was started approximately two months after the onset of the reaction to gold. Complete subsidence of the skin and mucosal lesions ensued following the administration of 3.30 gm. of BAL.

*Case 3.* Mrs. E. C., a white woman 67 years of age, was first seen on January 27, 1945, because of pains in the shoulders, arms, hips, and knees of one year's duration. Examination revealed a pallid, sick woman with generalized joint stiffness and periarticular soft tissue swelling of many joints typical of rheumatoid arthritis. This was superimposed upon a preëxisting degenerative arthritis. There was also evidence of calcareous aortic stenosis and insufficiency, but without myocardial decompensation. The blood count showed a marked hypochromic anemia, and the sedimentation rate was accelerated to 28 mm. in 60 min. (Cutler method). Roentgenograms of the spine and the sacro-iliac joints showed changes typical of an advanced Marie-Strumpell spondylitis; roentgen-rays of the left shoulder and hips were negative.

In addition to systemic management and physiotherapy, aurothioglycolanilide (Lauron) was administered, the initial dose being .050 gm. with gradual increase in the dose until a maximum of .300 gm. to .400 gm. was given weekly. This was continued from February 6, 1945, until September 18, 1945, at which time a total of 5.950 gm. had been given. Although there was evidence of moderate improvement in the arthritis, the sedimentation rate remained accelerated, being 25.5 mm. in 60 min. (Cutler method).

One week after administration of gold was discontinued, the patient developed a generalized dermatitis which rapidly progressed into a severe generalized exfoliative dermatitis. Except for the face and gluteal regions, the entire skin surface was markedly erythematous, itchy, and scaly with many fissures and exudation of serum. Soothing applications were applied to the skin, but the dermatitis remained practically unchanged for nearly a year. On August 11, 1946, the patient was admitted to the Montefiore Hospital because of mild congestive failure which was readily controlled by digitalis.

Although by September 22, 1946, the dermatitis was slightly improved, the patient was readmitted to the Montefiore Hospital for treatment with BAL. On September 23, 1946, .150 gm. of BAL was administered every four hours for 12 doses, followed by .100 gm. to .150 gm. twice daily. By September 28, five days following the in-

stitution of treatment with BAL, after a total of 3.0 gm. had been administered, improvement of the dermatitis was clearly perceptible, the most striking change being marked reduction in the degree of erythema and fissuring of the skin, with consequent diminution in the amount of oozing of serum. We could observe no change in the tendency to desquamation. Subsequent administration of an additional 2.1 gm. of BAL from September 28 to October 8, resulted in no further improvement of the dermatitis.

This case of severe generalized exfoliative dermatitis of one year's duration resulting from treatment with a slowly-absorbed gold salt was intractable to all previous therapy. With the administration of 3.0 gm. of BAL over a period of five days, improvement in the dermatitis, but not complete subsidence, occurred, evidenced by decrease in the degree of erythema and cessation of oozing of serum. Administration of additional BAL did not induce any further improvement.

*Case 4.* Mrs. G. McG., a white woman 42 years of age, was first seen on September 31, 1942, with an early rheumatoid arthritis. There was puffiness and stiffness of the finger joints, hypochromic anemia, and infected tonsils. The sedimentation rate was 18.5 mm. in 60 min. (Cutler method). Roentgenograms of both hands and knees were negative.

In addition to systemic measures and tonsillectomy, treatment with a soluble gold salt was instituted. From September 14, 1942, to October 26, 1942, she received a total of 335 gm. of aurothiomalate (Myochrysine) with no untoward reaction. There was some improvement both generally and in the joints.

She was not seen again until March 23, 1945, at which time there was evidence of marked reactivation of the arthritis. There were periarticular swelling and stiffness of the hands and knees, stiffness of the shoulders, many large subcutaneous rheumatic nodules, left axillary adenopathy, and hypochromic anemia. Biopsy of the left deltoid muscle showed on histological section islands of mononuclear cell infiltration, interstitial fibrosis and cloudy swelling of muscle fibers, such as have been described to occur in rheumatoid arthritis.<sup>6</sup> The sedimentation rate was 20 mm. in 60 min. (Cutler method). Systemic therapy and gold were resumed. This time aurothioglycolanilide (Lauron) was given, starting with .025 gm., with gradual increase in the dose until a maximum of .400 gm. was administered weekly. The latter dose was continued until August 6, 1945, at which time a total of 6.080 gm. of Lauron had been given. On August 13, 1945, slight pruritus and scaliness appeared involving the skin behind both ears. There was gradual progression of the dermatitis with involvement of the axillae and groins, then a more generalized erythema and scaling, and by January 30, 1946, the patient presented a severe exfoliative dermatitis with erythema, desquamation and oozing of serum. There was also evidence of a nephrosis; marked albuminuria with an occasional hyaline cast, but without cellular elements in the urinary sediment. The blood non-protein nitrogen was 31 mg. per cent; serum protein 5.36 gm. per cent; serum albumin 2.17 gm. per cent; and serum globulin 2.19 gm. per cent.

Except for minor fluctuations, the dermatitis remained more or less the same for a year. However, with general and local measures of treatment and repeated blood and plasma infusions, the dermatitis had cleared by August 29, 1946, leaving only residual pigmented areas. The nephrosis cleared entirely, leaving no apparent residue. The arthritis was completely arrested, all the subjective and objective manifestations having disappeared. Roentgenograms of both gluteal areas at this time showed remaining deposits of the heavy metal.

On October 22, 1946, there was a fresh mild recurrence of the gold dermatitis. Treatment with BAL was then started with a dosage of .150 gm. intramuscularly every four hours for two days, followed by .150 gm. twice daily for 10 days. At the end of this time, after approximately 4.8 gm. of BAL had been administered, the patient reported that the dermatitis was again largely cleared. She was seen again on January 24, 1947, at which time the skin rash was completely gone. The patient was still entirely free of subjective and objective manifestations of rheumatoid arthritis. The blood count, sedimentation rate, and urinalysis were entirely normal.

This patient developed a severe generalized exfoliative dermatitis and nephrosis following treatment with a slowly absorbed gold salt (Lauron). After one year's duration, both the dermatitis and nephrosis subsided completely. A mild recurrence of the dermatitis two months later was treated with 4.8 gm. of BAL, administered over a period of 10 days; complete clearing of the dermatitis ensued.

*Case 5.* Mrs. M. W., a white woman 59 years of age, was first seen on March 27, 1946, with rheumatoid arthritis of 20 years' duration. Examination revealed a pallid woman in considerable distress from arthritic pain. The joints showed changes typical of an advanced chronic rheumatoid arthritis. There was synovial and capsular thickening of the proximal interphalangeal joints of both hands and wrists, with flexion contractures and ulnar deviation of the fingers. Motion at both elbows was markedly limited, the knees and ankles were swollen, and there was considerable limitation in the range of motion in these joints. The sedimentation rate was accelerated to 25 mm. in 60 min. (Cutler method). Roentgenograms of both hands and knees showed destructive joint changes characteristic of an advanced rheumatoid arthritis.

In addition to the usual systemic measures and physiotherapy, treatment with aurothioglycolanilide (Lauron) was started, the initial dose being .050 gm., with gradual increase in the dose to a maximum of .200 gm. weekly. This was continued until August 20, 1946, at which time 4.350 gm. had been given, following which .200 gm. was administered every other week until December 9, 1946, until a total of 5.950 gm. had been given. At this time there was remarkable improvement in the arthritis, estimated to equal approximately 75 per cent. The sedimentation rate had likewise improved to 16.5 mm. in 60 min. (Cutler method). On December 23, 1946, several small pruritic scaly patches were noted on the skin of the anterior chest and left thigh. Administration of gold was discontinued. Within a period of four weeks, however, the dermatitis became more marked, consisting of scaly patches over the trunk and right upper eyelid. At no time, however, was the skin reaction very distressing or disabling.

Administration of BAL was started on January 20, 1947, with a dosage of .150 gm. four times daily for two days, followed by .150 gm. once to twice daily, thereafter, until approximately 3.0 gm. of BAL had been administered. When the patient was seen again on January 27, 1947, and on February 25, 1947, there was only slight improvement in the dermatitis.

The dermatitis in this case followed the administration of a slowly absorbed gold salt (Lauron). Although the skin lesions were not extensive and BAL was started 28 days following the onset of the dermatitis, there was little apparent benefit from the use of BAL.

## DISCUSSION

The therapeutic response to administration of BAL in the first case of our series demonstrated vividly the prompt resolution of a severe gold stomatitis induced by a relatively soluble and quickly absorbed preparation of gold, namely aurothioglucose (Solganol B Oleosum). It should be pointed out that the total amount of gold administered was relatively small and that it was given in small divided doses. Although we cannot discuss in detail the possible mechanisms of gold intoxication, it is our impression that an inherent idiosyncrasy is probably responsible to a large extent, especially when toxicity appears after relatively small amounts of the drug have been given. In any event, in the light of our past experience with similar cases, a stomatitis such as this patient (Case 1) presented would have lasted many months. With BAL resolution of the stomatitis was so prompt and complete that we can have no doubt of the value of the treatment. It should be emphasized, however, that the gold salt administered in this case was not only a relatively soluble and readily absorbed preparation, but that treatment with BAL was instituted within a relatively short period of time (within 24 days) after appearance of the first signs of toxicity.

In the second case the toxic effects, consisting of both skin and mucous membrane lesions, followed the administration of aurothioglycolanilide (Lauron), a much less soluble and more slowly absorbed gold salt. The conjunctivitis and anal ulceration persisted without any substantial improvement for approximately 10 weeks. Following the administration of BAL the mucosal lesions, as well as the dermatitis, cleared completely within less than a month. Although the possibility of spontaneous subsidence of these lesions cannot be entirely excluded, their persistence until BAL was administered and their prompt disappearance following the exhibition of this drug, makes us feel that BAL was instrumental in reversing the toxic effect.

In the third patient (Case 3) we feel that the use of BAL was effective in inducing some healing of the more acute manifestations of a generalized exfoliative dermatitis resulting from treatment with Lauron. The residual lichenification and scaling may have been the result of long standing damage to the skin. In the fourth patient (Case 4) recurrence of the dermatitis after apparent recovery may be presumed to have been caused by release of gold from depots at the sites of injection in the gluteal regions or by gold which had been stored elsewhere in the body. In any case, the prompt recovery from the reactivated dermatitis, in contrast with the protracted course of the dermatitis during the initial phase of the toxic reaction, may be related to the prompt administration of BAL. However, in view of the subsidence of the previous dermatitis, we cannot be sure that spontaneous recovery might not have occurred.

Although the dermatitis resulting from Lauron in Case 5 was mild in character and BAL was started within a relatively short period of time after the appearance of the skin reaction, treatment with BAL was ineffective.

We can offer no certain explanation for this disappointing result. Whether the persistence of the dermatitis was related to continued active absorption of gold from the injected sites can only be conjectured. If that is true, it is possible that the partial improvement noted in the long standing cases of dermatitis caused by Lauron (Cases 3 and 4) was due to the fact that the residual depots of gold were partially encapsulated by fibrous tissue so that further absorption was precluded or at least markedly slowed. It appears, therefore, that the striking effectiveness of BAL in the case of toxicity from aurothioglucose might have been the result of both the early administration of BAL and the solubility and rapidity of absorption of the gold salt preparation, whereas the partial effectiveness or total ineffectiveness of BAL in the other instances treated, caused by Lauron, were related to the less soluble quality of the drug or the duration of the dermatitis, or both.

It should be pointed out that the incidence of intoxication from the two preparations of gold mentioned in this small series treated with BAL does not reflect the actual relative toxicity of these two preparations.

Although we have been favorably impressed with the response to the administration of BAL in the first two cases cited and feel that BAL may have had some ameliorating effect in the third and fourth cases as well, we realize that the number of cases available for this report is too small to warrant final conclusions as to the effectiveness of BAL in the treatment of gold toxicity. The results do suggest, however, that in BAL we may have an agent that may prove valuable in the treatment of some of the toxic complications resulting from the therapeutic administration of gold. Further trial of BAL is certainly warranted in such instances.

#### SUMMARY AND CONCLUSIONS

Five cases of toxic reactions resulting from the therapeutic administration of gold in rheumatoid arthritis were treated with BAL (2,3-dimercaptopropanol).

In two cases BAL appeared to be of distinct benefit. In one of these a severe stomatitis from the administration of aurothioglucose (Solganol B Oleosum) responded dramatically. In the other patient, a mild conjunctivitis, anal ulceration and dermatitis resulting from aurothioglycolanilide (Lauron) cleared entirely.

In two cases of long standing generalized exfoliative dermatitis resulting from aurothioglycolanilide (Lauron) BAL appeared to have induced amelioration of the dermatitis.

In the fifth case, a mild dermatitis resulting from the administration of aurothioglycolanilide (Lauron), no appreciable benefit from the use of BAL could be noted.

Early use of BAL in the treatment of toxic effects resulting from the administration of gold appears to be of value.

Since the writing of this paper several publications on the use of BAL for gold intoxication have appeared.<sup>7</sup>

### BIBLIOGRAPHY

1. MARGOLIS, H. M.: Diagnosis and treatment of arthritis and allied disorders, 1941, Paul B. Hoeber, New York.  
 COMROE, B. I.: Arthritis and allied conditions, 1944, Lea and Febiger, Philadelphia.  
 STEINBROCKER, O.: Arthritis in modern practice, 1941, W. B. Saunders, Philadelphia.
2. EAGLE, H., MAGMESON, H. J., and FLEISHMAN, R.: The systemic treatment of experimental arsenic poisoning (mapharsen, lewisite, phenyl arsenoxide) with BAL, Jr. Clin. Invest., 1946, xxv, 451.  
 CARLETON, A. B., PETERS, R. A., STOCKEN, L. A., THOMPSON, R. H. S., and WILLIAMS, D. I.: The treatment of complications of arsenotherapy with BAL, Jr. Clin. Invest., 1946, xxv, 497.  
 LONGCOPE, W. T., LUETSCHER, J. A., JR., WINTROBE, M. M., and JAGER, V.: The treatment of arsenical dermatitis with preparation of BAL, Jr. Clin. Invest., 1946, xxv, 528.  
 GILMAN, A., ALLEN, R. P., PHILIPS, F. S., and ST. JOHN, E.: The treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbitol, and BAL glucoside, Jr. Clin. Invest., 1946, xxv, 549.  
 LONGCOPE, W. T., and LUETSCHER, J. A., JR.: The treatment of acute mercury poisoning by BAL, Jr. Clin. Invest., 1946, xxv, 557.
3. PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H. S.: British anti-Lewisite (BAL), Nature, 1945, clvi, 601.
4. EAGLE, H., MAGMESON, H. J., and FLEISHMAN, R.: The systemic treatment of experimental arsenic poisoning (mapharsen, Lewisite, phenyl arsenoxide) with BAL, Jr. Clin. Invest., 1946, xxv, 451.
5. Editorial, BAL in the treatment of arsenic and mercury poisoning, Ann. Int. Med., 1946, xxv, 986.
6. FREUND, H. A., STEINER, G., LEICHTENTRITT, B., and PRICE, A. E.: Nodular polymyositis in rheumatoid arthritis, Science, 1945, ci, 202.
7. COHEN, A., GOLDMAN, J. and DUBBS, A. W.: The treatment of acute gold and arsenic poisoning, use of BAL (2,3-dimercaptopropanol, British anti-Lewisite) Jr. Am. Med. Assoc., 1947, cxxxiii, 749.  
 RAGAN, C., and BOOTS, R. H.: The treatment of gold dermatitides, use of BAL (2,3-dimercaptopropanol), Jr. Am. Med. Assoc., 1947, cxxxiii, 752.  
 LOCKIE, L. M., NORCROSS, B. M., and GEORGE, C. W.: Treatment of two reactions due to gold, response of thrombopenic purpura and granulocytopenia to BAL therapy, Jr. Am. Med. Assoc., 1947, cxxxiii, 754.

# THE ORIGIN AND THE PHYSIOLOGY OF HEPARIN: THE SPECIFIC THERAPY IN THROMBOSIS \*

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*The Chemistry of Heparin.* A few years after the discovery of heparin by McLean<sup>1</sup> in 1916, while working under Howell, the latter author found that heparin gives a color reaction for uronic acids.<sup>2</sup> When the Toronto School at the Connaught Laboratories, in 1933,<sup>3</sup> had solved the problem of preparing larger quantities of heparin directly from fresh organs, I succeeded, in 1935,<sup>4</sup> in identifying heparin, as a mucopolysaccharide resembling the chondroitin sulfuric acid of the cartilage. The strongest heparin samples were found to contain about 26 per cent of a uronic acid and about 23 per cent of glucosamine, these components together making up about 90 per cent of the organic skeleton of heparin. On this occasion, the observation was made that heparin contains ester sulfuric acid, and surprisingly enough, not only one group to each disaccharide unit, as in chondroitin sulfuric acid, but three groups making up not less than 45 per cent of the weight of the free acid. Opinion is now unanimous with regard to these facts.

The uronic acid in heparin is claimed to be glucuronic acid.<sup>5</sup> Opinions still differ as to whether heparin contains an acetyl group or not. All the other known polysaccharides containing an amino sugar are acetylated at the amino group. In heparin also there is no free  $\text{NH}_2$ -group. Acetic acid, however, cannot be obtained from heparin by applying the ordinary methods of analysis, except for a small quantity, 10 to 15 per cent of the calculated amount—which could possibly be derived from impurities in the heparin preparations. The accompanying polysaccharides namely, split off acetic acid easily, and heparin is very difficult to purify. It is, in fact, doubtful whether any homogeneous pure samples of heparin have ever been prepared.

The whole discussion on the acetyl content of heparin has so far been founded on erroneous analytical data as well from our laboratory as from those of other workers.

There are thus many details as to the chemistry of heparin which are still uncertain. It will also be necessary to find out whether heparin is a definite chemical compound or whether it is a mixture of di- and trisulfuric acid esters of one and the same polysaccharide having a composition similar to that of Karl Meyer's hyaluronic acid. All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid.<sup>6, 7, 8</sup>

*The Mechanism of Action of Heparin.* The physico-chemical properties of heparin are quite unique. It has a high molecular weight and carries an

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exceptionally strong electric charge, apparently the strongest of all the organic compounds of the animal body. The strongest preparations, which contain 13.6 per cent of sulfur in the sodium salt, consist of no less than 45 per cent of sulfuric acid, really a peculiar product of synthesis in the living organism. The strongest compounds of a similar nature hitherto known, the nucleic acids, contain only 25 per cent of phosphoric acid. The high content of ester sulfuric acid is the most outstanding feature in the structure of heparin. *The sulfuric acid is as good a prosthetic group as any.* There are no other known reactive groups. All chemical findings therefore point in the direction that the anticoagulant activity is exerted through the electric charges of the high molecular polysaccharide.<sup>9</sup> The same is the case with the physiological findings.

Heparin has a multiple effect, acting not only on the components of the coagulation system, on the thrombin, the prothrombin, and the thrombokinase, but also on many other systems. It neutralizes the serum complement interfering in the Wassermann reaction. It reduces the isoagglutinin titer of the serum and it acts on different enzymes, preventing their action. In larger concentration (1 mg. per ml.) it also acts on the plasma proteins, strongly influencing the sedimentation rate of the red blood corpuscles. This multiplicity in its action can most easily be explained as a physico-chemical action of the acidic polysaccharide on the different proteins concerned. It is also known that the interaction between heparin and thrombin is reversible and very loose, it being reversed by adding an excess of thrombokinase.

It is known that lecithin and nucleic acids are capable of influencing the electric charge of proteins, moving their isoelectric point to the acidic side. Anionic i.e. acidic detergents, like dodecyl sulfate, act upon proteins even on the alkaline side of the isoelectric range, where the proteins are acids, acting upon the basic charges still present in the anionic protein. *It is a most interesting fact that the very few synthetic organic chemicals we knew of earlier, which acted directly as anticoagulants, such as Liquoid Roche and some diazo dyes, were all sulfonic esters of high molecular compounds.* All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid. Nature, in synthesizing heparin, has applied the same principle, and has done it in an excellent way, *the product being not only highly active but also non-toxic.* Even the polysaccharide polysulfuric esters so far prepared by various authors have more or less toxic properties.

The most convincing proof for the action mechanism of heparin was obtained through the finding of Chargaff and Olson<sup>10</sup> (1938) that protamine instantaneously abolishes the heparin effect in vitro and in vivo. Its electric charge neutralizes the negative electric charge of heparin.

Protamine sulfate, 50 to 100 mg., can be injected intravenously in man in 1 per cent sterile solution. The coagulation time of the blood is thereby instantaneously brought down to normal.

It has recently been found by Seegers that the prothrombin cannot be

absorbed on magnesium hydroxide if heparin is present. Evidently the physico-chemical state of the prothrombin is altered.

A physico-chemical mechanism of action seems therefore to be the most probable.

There are facts, however, not so easy to explain. Thus Jaques<sup>11</sup> found dog heparin to have a two and one-half times stronger anti-coagulant effect than the same amount of ox heparin, whereas pig and sheep heparins are much weaker. They all have the same content of ester sulfuric acid. His findings have later been fully confirmed.

*The osmotic properties of heparin* show a very interesting feature. In spite of a strong ionic dissociation, it exerts an extremely low osmotic pressure in aqueous solution.

This is the same phenomenon which E. Hammarsten<sup>12</sup> (1924) studied in another strongly acidic compound of high-molecular weight, the thymonucleic acid of cell nuclei. Both these substances, heparin and the thymonucleic acid, in aqueous solution show only a fraction of the osmotic pressure which the degree of ionization would lead one to expect. The salts of heparin exert less than a tenth of the calculated osmotic pressure. The phenomenon involves an interesting protective mechanism which nature has developed to avoid high osmotic pressure and the resulting displacement of fluid when compounds with a high electric charge are deposited in cells. Otherwise, no nucleic acid could be stored in the cell nuclei, nor any heparin in the heparin-producing cells. The nuclei and the cells would be disrupted by the water entering them from outside in order to establish osmotic equilibrium on both sides of the nuclear and cellular membrane respectively. The sodium or potassium ions bound to the high molecular negative complexes of heparin and the nucleic acids respectively do not exert any osmotic pressure although they occur as ions. They have disappeared "im Lebensraum des grossen Molekuls." When someone disappears into the living space of the more powerful ones, having an opposite charge, he has, indeed, very little say. It is not without interest to observe how Nature, when life's conditions so demand, has put out of function one of the most fundamental natural laws, that of the osmotic pressure of salt solution.

This lack of osmotic pressure makes heparin very useful in blood analysis, because it does not cause shrinkage of the red blood corpuscles. It is the only anticoagulant to be used in hematocrit determinations. A concentrated 5 per cent solution of heparin can also, without any drawbacks, be injected undiluted into the blood.

*Heparin and the Ehrlich Mast Cells.* The unusual physico-chemical properties of heparin show another peculiarity. Heparin gives an extraordinarily strong metachromasia, a purple violet staining with certain blue basic dyes.

At a time when the sulfur content of heparin was denied by several authors, it was possible to demonstrate that it gave an exceedingly strong

violet metachromatic reaction with toluidine blue,<sup>13</sup> a reaction which a Belgian histologist, Lison,<sup>14</sup> had shown in 1935 to be given only by high molecular esters of sulfuric acid. The metachromasia of the cartilage is due to the chondroitin sulfuric acid. Heparin gives a 100 times stronger metachromasia than does this acid. By means of this reaction, we were able to demonstrate in 1937, together with Holmgren and Wilander,<sup>15, 16</sup> that heparin is produced by the mast cells of Ehrlich.

In 1933 Quensel,<sup>17</sup> Professor Emeritus of Pathology at Uppsala in Sweden, published a paper on these cells. Summarizing the results of a study of human material, he concluded that he—like Staemmler before him—regarded the mast cells as unicellular glands of the connective tissue.

He found the topography of the mast cells very characteristic, with an accumulation close to the walls of the smallest blood vessels and the capillaries. The perivascular position is so regular and consistent that it is an essential feature of the topography of the mast cells, and cannot be regarded as accidental. "This appearance is so consistent that it must have some relation to the hitherto unknown function of the mast cells." Four years later we were able to explain this relationship.

The mast cells, because of their position around capillaries and the small blood vessels without a muscular coat, are able to void their granular contents into the peripheral tissue juices, or almost directly into the blood stream, a state of affairs which indicates that these cells—and with them the heparin—may have a physiological function to fulfill. The mast cells evidently form a hormonal system, with the cells widely distributed around the capillaries in the body.

The close connection between the mast cells and the blood vessels has recently been demonstrated in different ways. We were also previously aware that the mast cells follow the capillaries, that neoplastic and inflammatory tissues rich in capillaries are also rich in mast cells. Recently, Holmgren—who did the histological part of our common work on the mast cells—has shown that there is a steady and very considerable decrease during the course of life. This reduction in number of the mast cells corresponds to the reduction of the capillaries with increasing age.

A most interesting increase in the mast cell content of the tissues was observed in the victims of Hiroshima. A general bleeding tendency was observed in the survivors as a consequence of the irradiation. Histologists stated that there was a general increase of the mast cells in the tissues of the victims. A similar condition with hyperheparinemia has recently been produced by Garrott Allen<sup>18</sup> in Chicago through roentgen-ray irradiation of dogs.

We also have a disease, urticaria pigmentosa, with multiple petechial hemorrhages in the skin in which the pathologists long ago stated that there are abnormal local accumulations of mast cells in the skin.

Recently, Robert Ehrstrom, in Finland, suggested that these cells should

be named heparinocytes, which is of course a nomination much more convenient than the German name "Mastzellen."

Before leaving the discussion about the mast cells, which we now know produce heparin, I feel that we should pay a tribute to Ehrlich for his introduction of the specific stains which he himself used so successfully. With them, he succeeded in staining the granules of the leukocytes, different bacteria and also—in using methyl violet and basic saffranine—to separate the mast cells from Waldeyer's plasma cells. When he did this, 70 years ago, he could hardly have anticipated that his specific stains—in this case toluidine blue—would in due time enable us to demonstrate the natural anticoagulant at the site of its formation.

*Heparin in Thrombosis.* For the medical profession the most important question is to what extent this natural anticoagulant can be used in thrombosis. As late as 1934 the great German clinician, Morawitz, confessed that we were at that time as helpless against thrombosis as fifty years ago, and that real progress in that field was not to be expected "unless we are able to influence not only the mechanical factors but also the fundamental processes of the blood which induce coagulation and thrombosis." In the meantime, Homans and his associates<sup>19</sup> have shown that a mechanical procedure, the venous interruption, the ligation of the femoral vein, is quite effective in combating pulmonary embolism. The specific treatment by influencing the coagulation mechanism is now also at our disposal. The coagulation tendency of the blood can be controlled in vivo. This can be achieved not only by means of heparin, the physiological anticoagulant of the body itself, but also thanks to the excellent work of Dr. Link<sup>20</sup> and his associates in this country, by eliminating the prothrombin production by means of dicumarol. These anticoagulants have now proved effective both for the prevention and treatment of thrombosis and pulmonary embolism.

Simultaneously and independently Crafoord<sup>21</sup> in Sweden and Gordon Murray<sup>22</sup> in Canada showed during 1935–1942 that thrombosis can be prevented if heparin is given post-operatively in sufficient amounts, 250 to 325 mg. a day, until the patient is out of bed. About 800 cases were reported from Sweden and half the number from Canada. Practically no thrombo-embolic complications occurred, although a frequency of 2 to 4 per cent could have been expected. Similar good results have been reported in using dicumarol, which has been given to more than 1000 cases prophylactically at the Mayo Clinic<sup>23</sup> and to 1500 cases at Lund in Sweden.<sup>24</sup>

The cost of the treatment and the labor involved, however, preclude a general application of the prophylaxis with anticoagulants. There is also a pronounced bleeding tendency from the field of operation. In spite of these drawbacks, *anticoagulants are to be given prophylactically after operations or childbirth where there have been single or recurrent attacks of thrombosis in the history of the patient.*

We already have a quite extensive experience with the use of heparin

alone or in conjunction with dicumarol in thrombosis. Already in their first papers on the use of heparin in man, Murray and Best <sup>25</sup> in 1938, and Murray and MacKenzie <sup>26</sup> in 1939, reported on a number of cases of spontaneous thrombo-phlebitis and pulmonary embolism treated with heparin. The acute symptoms disappeared in a surprisingly short time. There was no spreading to the other leg, nor were there any recurrences of pulmonary embolism. The anticoagulant therapy was combined with free active movements.

In Sweden, Gunnar Bauer has shown particular interest in this question. In 1940,<sup>27</sup> he found that an incipient thrombosis in the lower part of the leg was checked in its growth by heparin treatment, combined with free movements and early ambulation. The patients could leave the bed in four to six days.

Anticoagulant therapy is at present routine in Sweden in cases of ordinary leg thrombosis and pulmonary embolism. In some clinics only heparin is used, in most of the clinics it is given in conjunction with dicumarol.

Heparin has been given in three or four daily intravenous injections, 100 to 125 or 150 mg. each time. Usually 350 to 450 mg. of a sodium salt with 80 Toronto units per milligram are given a day. The effect is not controlled by any blood analyses except for special cases, e.g. elderly persons with impaired renal function. Consequently heparin treatment can be given at any hospital, even the smallest ones, and if necessary, at the home of the patient. The bleeding tendency is not very pronounced.

Bauer <sup>28</sup> himself has reported on 260 cases treated with heparin during the last six years, and in 1945, Zilliacus <sup>29</sup> collected 600 cases of thrombosis or pulmonary embolism from 20 different clinics, most of them treated with heparin.

Summarizing the results, it can be said that the thrombotic process is effectively checked, if the anticoagulants are given in an adequate dose. The recumbency time is shortened to one week or less from six weeks. The mortality is practically nil, from being earlier 5 per cent in obstetric cases and 20 per cent in surgical and medical cases. The effect of the treatment is so consistent that it is necessary to search for an error in the treatment or to consider another diagnosis if the patient does not respond favorably to the treatment.

As to the results of the anticoagulant therapy, there is one more detail of special importance. The sequelae usually following thrombosis, swollen legs, indurations, pain, eczema and ulcers, can be prevented if the thrombosis is checked early while still confined to the calf. This detail has been particularly stressed by Bauer.<sup>30</sup> In a study of 1300 cases of leg ulcers, Birger,\* in Sweden, recently found the ulcers to be caused by a previous thrombosis in not less than 40 per cent of the cases. Likewise, Zilliacus \* last year made a follow-up examination of 680 patients, who had suffered from a thrombosis

\* Unpublished communication.

6 to 14 years earlier. Ninety per cent of them had more or less severe troubles with their legs; more than 50 per cent had chronic induration and eczema of the leg; 20 per cent had leg ulcers, chronic or recurrent; and an equal number had similar changes in the other leg. One in 10 of the patients had become completely disabled, incapable of any work.

The cases treated with heparin in an early stage of the disease have, on follow-up examination, shown quite a different picture. Where the process had been confined to the calf, the leg had usually remained normal. Much suffering and social disablement could consequently be avoided if the cases with spontaneous deep venous leg thrombosis were diagnosed in time and immediately given an adequate therapy. At least during the first days is heparin to be given.

The use of the anticoagulants is, however, not confined to the treatment of leg thrombosis and pulmonary embolism. Its use in other thrombotic conditions and in vascular surgery has been discussed in a recent monograph.<sup>31</sup>

Most interesting observations have recently been made as to the cause of some non-virus pneumonias with a protracted course and resistant to antibiotics. Here heparin and dicumarol often have a quite specific effect. There may be a rise in temperature lasting for weeks, blood stringed sputum and diffuse symptoms from the lungs, resistant to sulfa and penicillin therapy. As soon as heparin and dicumarol are given, recovery follows within a few days.\* Latent thrombi, e.g. in the pelvic veins giving pulmonary infarctions, are far more common than suspected in these cases. The anticoagulant therapy not only clears up the diagnosis but also protects the patients from recurrent pulmonary embolisms.

The possibility of checking the fibrin formation by means of anti-coagulants will certainly be extensively studied in different disease conditions where it is desirable to prevent further fibrin formation in the capillaries and their vicinity, e.g. in allergic and acute rheumatic conditions. This is demonstrated in the following case.\* A woman who had received repeated blood transfusions developed Rh-immunization. After a renewed transfusion she manifested a hemolytic shock, with oliguria developing overnight into anuria. The following day she got 125 mg. of heparin three times. Within two hours after the first injection she excreted 400 ml. of urine. In the next 12 hours the excretion was 1200 ml.

Our results in applying anticoagulants, mainly heparin in thrombosis in Sweden during the last six years are clearly demonstrated in the following three tables. Table 1 comprises the material of Bauer. Table 2 shows the change in mortality following the introduction of the anticoagulant therapy in different clinics during 1940 to 1944 and table 3 shows the 900 cases of deep venous thrombosis or pulmonary embolism, treated mostly with heparin and some of them with heparin and dicumarol, reported by Bauer and Zilliacus together.

\* S. Kallner: Unpublished communication.

TABLE I  
Heparin Treatment of Thrombosis and Pulmonary Embolism at the  
Mariestad Hospital, Sweden, 1940-1946

	No Treatment 1929-1938	Heparin Treatment October 1, 1940- September 30, 1946
Number of patients admitted	25,628	20,002
Number of thrombosis cases	264	258*
Fatal embolism	47	3
Mortality in thrombosis cases	18 p.c.	1.1 p.c.
Average duration of stay in bed	40 days	4.6 days
Disabling after-effects	Serious	None or very slight

\* 104 patients were admitted to the Mariestad Hospital on account of thrombosis.

TABLE II

Series of Thrombotic Cases Treated with Anticoagulants, mainly Heparin, during 1940-1944

	Without Anticoagulants		With Anticoagulants	
	Cases	Deaths	Cases	Deaths
Med. Clinic A	16	9	22	0
Surg. Clinic A	71	17		
Surg. Clinic B	41	5	26	0
Surg. Clinic C			74	0
Surg. Clinic D	33	11	31	1
	161	42	153	1

TABLE III

Mortality in Cases of Thrombosis or Pulmonary Infarction (Bauer, Zilliacus)

	Cases	Deaths	Per cent
Conservative treatment	543	88	16
Heparin	769	5	0.67
Dicumarol	131	1	

To these 900 carefully controlled cases of thrombosis or pulmonary embolism from Sweden can be added 371 cases of thrombophlebitis of the deep veins and 149 cases of pulmonary embolism, in total 520 cases treated with heparin in Canada and reported by Murray in 1946,<sup>82</sup> among which no fatal cases occurred.

The results obtained in using heparin have been successfully supplemented by the experiences in using dicumarol as reported from the Mayo Clinic.<sup>33, 34</sup>

The results in using anticoagulant therapy are as striking as any hitherto reported following the introduction of a specific therapy in medicine.

Since this very month is the centenary of the introduction by Semmelweis at the Maternity Clinic of the Allgemeines Krankenhaus in Vienna of his new principle for the prevention of death in puerperal fever, I take the opportunity

of reminding you about this milestone in medicine. In May 1847, he prescribed ordinary washing of the hands, followed by rinsing with chlorinated water, in order to prevent the transfer of the contagion or the miasma which he believed caused puerperal fever. His results were as follows:

TABLE IV

Years	Patients	Deaths Per cent
1846	3,354	13.6
1847	3,375	5.2
1848	3,356	1.3

*Mutatis mutandis*, we have achieved equally good results as Semmelweis did in our efforts to treat another serious complication following childbirth and operations. We are now evidently able to control the course of the thrombo-embolic disease, not only by mechanical means but also as Morawitz hoped, by checking the fundamental processes of the blood which induce coagulation and thrombosis.

## BIBLIOGRAPHY

1. McLEAN, J.: The thromboplastic action of cephalin, *Am. Jr. Physiol.*, 1916, xli, 250.
2. HOWELL, W. H.: The purification of heparin and its chemical and physiological reactions, *Bull. Johns Hopkins Hosp.*, 1928, xlii, 199.
3. CHARLES, A. F., and SCOTT, D. A.: Studies on heparin, *Jr. Biol. Chem.*, 1933, cii, 425, 437.
4. JORPES, J. E.: On the chemistry of heparin, *Biochem. Jr.*, 1935, xxix, 1817.
5. WOLFROM, M. L., and RICE, F. A. H.: The uronic acid component of heparin, *Jr. Am. Chem. Soc.*, 1946, xlviii, 532.
6. BERGSTRÖM, S.: Ueber die Wirkungsgruppe des Heparins, *Naturwiss.*, 1935, xxiii, 706.
7. CHARGAFF, E., BANCROFT, FR. W., and STANLEY-BROWN, M.: Studies on the chemistry of blood coagulation, *Jr. Biol. Chem.*, 1936, cxv, 149, 155.
8. KARRER, P., USTERI, E., and CAMERINO, B.: Ueber blutgerinnungshemmende Stoffe, *Helv. Chim. Acta*, 1944, xxvii, 1422.
9. JORPES, J. E.: Ueber die Wirkungsweise des Heparins, *Skand. Arch. Physiol.*, 1938, lxxx, 202.
10. CHARGAFF, E., and OLSON, K. B.: The influence of protamine on the anticoagulant effect in vivo, *Jr. Biol. Chem.*, 1938, cxxii, 153.
11. JAQUES, L. B.: Heparins of various mammalian species and their relative anticoagulant potency, *Science*, 1940, xcii, 488.
12. HAMMARSTEN, E.: Zur Kenntnis der biologischen Bedeutung der Nucleinsäureverbindungen, *Biochem. Ztschr.*, 1924, cxliv, 383.
13. JORPES, J. E.: On heparin, its chemical nature and properties, *Acta med. Scand.*, 1936, lxxxviii, 427.
14. LISON, L.: La signification histochemique de la métachromasie, *Compt. rend. Soc. d. biol.*, 1935, cxviii, 821.
15. HOLMGREN, HJ., and WILANDER, O.: Zur Kenntnis der Chemie und Funktion der Ehrlichschen Mastzellen, *Ztschr. mikr.-anat. Forsch.*, 1937, xlii, 242.
16. JORPES, J. E., HOLMGREN, HJ., and WILANDER, O.: Ueber das Vorkommen von Heparin in den Gefäßwänden und in den Augen, *Ztschr. mikr.-anat. Forsch.*, 1937, xlii, 279.
17. QUENSEL, U.: Studien über die Gewebsmastzellen, *Acta path. microbiol. Scand.*, 1933, Suppl. xvi, 358.
18. ALLEN, J. G., and JACOBSON, L. O.: Hyperheparinemia: cause of hemorrhagic syndrome associated with total body exposure to ionizing irradiation, *Science*, 1947, cv, 388.



19. ALLEN, A. W.: Interruption of the deep veins of the lower extremities in the prevention and treatment of thrombosis and embolism, *Surg., Gynec. and Obst.*, 1947, lxxxiv, 519.
20. LINK, K. P.: The anticoagulant from spoiled sweet clover hay, *Harvey Lectures*, 1943-44, 162.
21. CRAFTOORD, C., and JORPES, J. E.: Heparin as a prophylactic against thrombosis, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2831.
22. MURRAY, G., and MACKENZIE, R.: Postoperative thrombosis and embolism, *Am. Jr. Surg.*, N. S. 1942, lvii, 414.
23. BARKER, N. W., CROMER, H. E., HURN, M., and WAUGH, J. M.: Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration, *Surgery*, 1945, xvii, 207.
24. BRUZELIUS, S.: Dicoumarin in clinical use: Studies on its prophylactic and therapeutic value in treatment of thrombo-embolism, *Acta chir. Scandin.*, 1945, xcii, Suppl. 100.
25. MURRAY, G., and BEST, C. H.: The use of heparin in thrombosis, *Ann. Surg.*, 1938, cviii, 163.
26. MURRAY, G., and MACKENZIE, R.: The effect of heparin in portal thrombosis. Its use in mesenteric thrombosis and following splenectomy, *Canad. Med. Assoc. Jr.*, 1939, xli, 38.
27. BAUER, G.: A venographic study of thrombo-embolic problems, *Acta chir. Scandin.*, 1940, lxxxiv, Suppl. 61.
28. BAUER, G.: Heparin therapy in acute deep venous thrombosis, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 196.
29. ZILLIACUS, H.: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the postthrombotic sequelae. The results of five years' treatment of thrombosis and pulmonary embolism at a series of Swedish hospitals during the years 1940-1945, *Acta med. Scandin.*, 1946, Suppl. 171.
30. BAUER, G.: The sequelae following leg thrombosis, *Acta chir. Scandin.*, 1942, lxxxvi, Suppl. 74.
31. JORPES, J. E.: Heparin in the treatment of thrombosis, *Monograph*, Oxford Univ. Press, 2 Ed., 1946.
32. MURRAY, G.: Anticoagulants in venous thrombosis and pulmonary embolism, *Surg., Gynec. and Obst.*, 1947, lxxxiv, 665.
33. BARKER, N. W.: Clinical use of dicumarol, *Med. Clin. North Am.*, 1945, xxix, 925 and *Minnesota Med.*, 1946, xxix, 778.
34. ALLEN, E. V., HINES, E. A., JR., KVALE, W. F., and BARKER, N. W.: The use of dicumarol as an anticoagulant: experience in 2,307 cases, *Ann. Int. Med.*, 1947, xxvii, 371.

## THE USE OF DICUMAROL AS AN ANTICOAGULANT: EXPERIENCE IN 2,307 CASES \*

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SIX years have elapsed since the first report on the clinical use of dicumarol.<sup>1</sup> Since that time there have been a number of clinical reports by ourselves and others. The literature has been reviewed previously.<sup>2,3</sup> It is the purpose of this presentation to consider this new therapeutic tool in the light of six years' experience.

Dicumarol is a pure chemical compound which may be recovered from spoiled sweet clover and which has been prepared synthetically. The discovery that it is the agent which causes spoiled sweet clover disease of animals which is characterized by hemorrhage, the determination of its chemical formula, the synthesis of it and other studies by Link and his associates mark an epoch in research which is admirably presented in the Harvey lectures for 1943-1944.<sup>4</sup> Dicumarol impairs coagulation of the blood, *in vivo*, by depressing the values for prothrombin. When used clinically it has no other significant effect, except that hemorrhage may result when the concentration of prothrombin in the blood is diminished too greatly. Dicumarol is not an ideal anticoagulant because its effect is delayed for one to two days after oral administration, because its effect persists for several days after discontinuance of administration and because judicious use requires the services of skilled and experienced laboratory personnel. Heparin, the only other anticoagulant available for clinical use, has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action (about three hours after injection). A further advantage is that it can be satisfactorily administered without "laboratory control." The disadvantages of use of heparin are the relatively great cost and the need for parenteral administration.

Heparin and dicumarol are not competitors for clinical use; the use of one complements the use of the other. In many instances they should be used together. Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value for prothrombin in the blood is not available. Although it may be given by continuous administration, the intravenous injection of 50 mg. of heparin (5 c.c. of solution) every four hours has been satisfactory for clinical use. Dicumarol should be used whenever an anticoagulant effect is needed over a

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period of days, weeks, months or years, provided that there are available reliable determinations of the value for prothrombin in the blood. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously; administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.\*

### THE DOSAGE OF DICUMAROL

The amount of dicumarol to be used depends entirely on the value for prothrombin in the blood after the drug has been administered on two successive days. In our studies we have attempted to maintain the values for prothrombin in the blood between 10 per cent and 30 per cent, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10 per cent and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30 per cent. It is possible that dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as much as we have indicated.

The inexperienced may be confused by the use of the terms "prothrombin time" and "prothrombin percentage"; they do not have the same significance nor do they have a linear relationship. The laboratory should furnish to the clinician a chart by means of which he may convert prothrombin time into prothrombin percentage.<sup>5</sup> According to the technic used at the Mayo Clinic, a normal prothrombin time is 17 to 19 seconds; a prothrombin time of 27 seconds signifies 30 per cent prothrombin; 35 seconds signifies 20 per cent prothrombin and 58 seconds indicates 10 per cent prothrombin. However, in other institutions where different thromboplastins or technics are used in the performance of the prothrombin time test, quite different prothrombin times may correspond to values for 100 per cent, 30 per cent, 20 per cent and 10 per cent prothrombin.

Three hundred milligrams of dicumarol are given on the first day and 200 mg. on the second day. On each subsequent day when the prothrombin is more than 20 per cent, 200 mg. are given. On any day when the value for prothrombin is less than 20 per cent, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol, which have been discussed in another publication.<sup>2</sup>

### THE DANGER OF HEMORRHAGE WHEN DICUMAROL IS USED

The sole danger associated with the use of dicumarol is hemorrhage. In our series of 1,983 postoperative cases minor hemorrhage (epistaxis, hematuria and localized ecchymosis) occurred in 3.4 per cent of cases and

\* When both heparin and dicumarol are used, blood for determination of the values for prothrombin should be drawn not less than three hours after the last injection of heparin, since heparin itself modifies the result of the test for prothrombin.

serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of cases. One may expect minor bleeding in about one of each 25 postoperative cases and serious bleeding in about one of each 50 postoperative cases. There is a great difference between serious bleeding and fatal bleeding. Although marked bleeding from operative wounds occurred about 40 times during the course of treatment of almost 2,000 patients who had undergone operation, death from hemorrhage occurred only twice. Careful study of the records of these two fatalities, reported in detail elsewhere, indicates that the fatal hemorrhage could not definitely be attributed to the effect of dicumarol.<sup>2</sup> However, the two fatalities emphasize the ever-present danger of hemorrhage when dicumarol is used.

### THE PREVENTION AND CONTROL OF HEMORRHAGE

The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage will occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg. and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hour intervals, once or twice as needed.

### CONTRAINDICATIONS TO THE USE OF DICUMAROL

We use dicumarol cautiously or refrain from its use in renal insufficiency, which prolongs and enhances the effect of dicumarol, after operations on the brain or spinal cord, because bleeding in these regions might result in disaster, in blood dyscrasias with increased tendency to bleed because dicumarol will accentuate the tendency to bleed, in ulcerative lesions because of the tendency to bleed, and in nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency. We doubt whether the use of anticoagulants adds anything to the treatment of subacute bacterial endocarditis and we do not use them in such cases, since the danger of hemorrhage is relatively great.

### EXPERIENCE IN 2,019 POSTOPERATIVE CASES \*

The results of treatment in 352 cases of postoperative venous thrombosis are shown in table 1. In 832 cases of abdominal hysterectomy dicumarol was given prophylactically (table 2) because experience has indicated that in 4 per cent of such instances venous thrombosis occurs following operation; death from pulmonary embolism occurs in 0.7 per cent. In 329 cases of pulmonary embolism after operation anticoagulants were used (table 3). In

\* In many instances of pulmonary embolism heparin and dicumarol were used. In most instances of venous thrombosis, dicumarol alone was used. In all instances in which an anticoagulant was used prophylactically, dicumarol only was used.

TABLE I

Results of Use of Anticoagulants in 352 Cases of Postoperative Venous Thrombosis

	Cases	
	Expected if Anticoagulants had not been Used*	Occurred
Subsequent venous thrombosis or pulmonary embolism	88	9†
Fatal pulmonary embolism	20	0

\* On the basis of the rates given in the reports of Barker, Nygaard, Walters and Priestley.<sup>47</sup>

† In 3 cases the percentage of prothrombin in the blood was more than 30. In 1 case use of dicumarol had been discontinued and prothrombin was normal.

TABLE II

Results of Prophylactic Use of Dicumarol in 832 Cases of Abdominal Hysterectomy

	Cases	
	Expected if Anticoagulants had not been Used	Occurred
Venous thrombosis or pulmonary embolism	33	3*
Fatal pulmonary embolism	6	0

\* Minor venous thrombosis.

TABLE III

Results of Anticoagulant Therapy in 329 Cases of Pulmonary Embolism

	Cases	
	Expected if Anticoagulants had not been Used	Occurred
Subsequent venous thrombosis or pulmonary embolism	144	3
Fatal pulmonary embolism	60	1*

\* Occurred after prothrombin time had returned to normal.

addition to the cases considered in tables 1, 2 and 3, there were 470 instances in which dicumarol was used prophylactically to prevent pulmonary embolism and venous thrombosis. These were instances in which venous thrombosis or pulmonary embolism had occurred after previous operations or in which the prospects of postoperative venous thrombosis were considered relatively great. Venous thrombosis occurred in two instances. There was no instance of pulmonary embolism.

In 36 additional cases dicumarol was used prophylactically after amputation of a leg because of arteriosclerosis obliterans or thrombo-angiitis obliterans; there were no vascular complications except that bleeding into the region of amputation occurred in one instance. Unfortunately no figures

are available for comparison of results with and without anticoagulants. We can indicate only that dicumarol provided adequate protection against venous thrombosis in these cases.

An over-all consideration of the 1,513 cases presented in tables 1, 2 and 3 indicates that the following results were achieved: 85 patients survived who might have been expected to die had anticoagulants not been used; 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. No great accuracy is claimed for these figures since alternate patients were not treated with and without anticoagulants; the control figures were calculated from experiences before anticoagulants were used. We recognize the deficiency in this method of study but the striking efficiency of anticoagulants in preventing pulmonary embolism and venous thrombosis is nonetheless impressive.

#### ADDITIONAL DISADVANTAGES OF ANTICOAGULANT THERAPY

In considering venous thrombosis and pulmonary embolism there is one, most desirable goal: absolute prevention. This has not been achieved. Table 2 illustrates the point well. Eight hundred thirty-two patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save six lives and in order to prevent venous thrombosis and nonfatal pulmonary embolism in 30 instances. The returns might be considered small. The numerical results are more impressive in cases of venous thrombosis and nonfatal pulmonary embolism; yet it was necessary, in the aggregate, to treat 681 patients in order to save 79 lives and to prevent further venous thrombosis and embolism in 220 instances. We do not belittle these results. We only emphasize our inability to detect the predisposition to venous thrombosis *before it occurs*. Were it possible to designate the patients who would have venous thrombosis *before they had it*, treatment with anticoagulants would be even more productive. There has been a good deal of study on this phase of the problem of venous thrombosis and embolism; some progress has been made on the periphery but the hard core of the problem remains.

#### COMMENTS ON LIGATION OF VEINS VERSUS USE OF ANTICOAGULANTS

Our experience with ligation of veins has been very limited. That is a natural result of the gratifying experiences with anticoagulants that we have had. Furthermore, we do not know of any results from ligation of veins which approach in excellence those derived from our experience with anticoagulants. It is well to remember that the sole purpose of ligation of veins is to prevent pulmonary embolism. Also ligation of a vein will prevent pulmonary embolism only from that region which is distal to the ligature. Thus if the surgeon ligates the left superficial femoral vein he will prevent pulmonary embolism only from the left leg distal to the ligature. It is common experience that in such instances pulmonary embolism may originate from the right leg or from a region proximal to the ligature on the left.

Anticoagulants are used for two purposes: to prevent pulmonary emboli from originating anywhere in the body and to prevent extension of venous thrombosis. While it is more impressive to prevent pulmonary embolism, the importance of preventing occurrence or extension of venous thrombosis must be stressed. Any physician, observing the varices, edema, stasis dermatitis and cellulitis, and varicose ulcers years after a patient has had post-operative venous thrombosis, can testify to that. There is some difference of opinion in surgical circles as to whether or not ligation of veins contributes to the chronic venous insufficiency which might ordinarily result from venous thrombosis. Certainly ligation does not lessen venous insufficiency as anticoagulants do by preventing extension of the thrombosis.

Our carefully considered opinion, after weighing available evidence, is that the use of anticoagulants is, in general, a much better method of treatment than ligation of veins. We recognize a small rôle for ligation of veins, which is, at times, quite important, but we do not recognize superiority of this method in the type of case which has been considered in this presentation.

#### ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

Three previously published reports by others indicate the usefulness of anticoagulants in acute myocardial infarction.<sup>8-10</sup> Fifty patients who had this condition have been treated at the Mayo Clinic; the detailed report by Parker and one of us is available elsewhere.<sup>11</sup> One hundred cases observed at our clinic previously, before the use of anticoagulants, served as the control series.<sup>12</sup> In 10 of our cases heparin and dicumarol were used; in 40 cases dicumarol alone was used. There were no instances of peripheral arterial embolism or venous thrombosis. Pulmonary embolism which did not cause death occurred in one instance (2 per cent) at a time when the prothrombin in the blood was not satisfactorily reduced. Five patients died (10 per cent). Evidence of further myocardial infarction occurred in one instance (2 per cent). There was only one instance of serious bleeding, hemarthrosis of a knee joint. In the control group the incidence of pulmonary embolism, peripheral arterial embolism and venous thrombosis was 33 per cent, the incidence of further myocardial infarction was 15 per cent and the death rate was 13 per cent.

No final conclusion can be drawn from experience with 50 cases nor from the other individual reports. However, in the aggregate the results seem significant. Certainly there is no evidence of harm resulting from the use of anticoagulants in acute myocardial infarction. Final decision relative to the value of this type of treatment must wait on extensive experience with a large number of cases, such as that now being obtained by a coöperative study under the supervision of Dr. I. S. Wright and the American Heart Association.

We believe that both heparin and dicumarol should be used in the treatment of acute myocardial infarction, that treatment should be begun as soon

as possible after the diagnosis has been made and that it should be continued for at least four weeks.

### ANTICOAGULANTS IN THE POSTPARTUM STATE

Previous reports indicate that dicumarol may be used safely and with benefit in the treatment and prevention of venous thrombosis following delivery.<sup>13, 14</sup> Indeed the first dose may be administered prophylactically during labor and administration may be continued during the postpartum state without inducing uterine hemorrhage.<sup>14</sup> Dicumarol may appear in the milk of lactating animals to which it is given; indeed baby rats nursing from mothers receiving dicumarol may bleed and die.<sup>15, 16</sup> However, the dose (5 mg. daily) given to the mother rats produced prothrombin deficiency in their blood and caused them to die in six to nine days. The dose administered to the rats was many times greater than that given to patients, if body weight is considered. No conclusions can be drawn from these studies except that if rats are given excessive amounts of dicumarol, their milk may contain sufficient dicumarol to produce profound prothrombin deficiency in nursing young. There is no clinical corollary to this situation.

We have administered heparin and dicumarol or dicumarol alone to 19 postpartum patients, *four* of whom had pulmonary embolism and 15 of whom had venous thrombosis in the legs. Four of these patients had undergone cesarean section. Treatment was begun as early as the fifth postpartum day to patients who had vaginal delivery and as early as the eleventh day following cesarean section. There was no unusual bleeding although the values for prothrombin in the blood were mostly between 10 per cent and 30 per cent after the third day of treatment. In no instance was there further venous thrombosis or pulmonary embolism. Only two mothers were nursing their babies while they received dicumarol. Repeated studies of the blood of each baby indicated that the values for prothrombin were never reduced significantly; they were consistently between 90 per cent of normal and normal, even when the values for prothrombin in their mothers' blood were between 10 per cent and 30 per cent.

Our studies support the conclusions of previously published reports that anticoagulants may be used after delivery, as needed for the prevention and treatment of pulmonary embolism and venous thrombosis. The problem of prothrombin deficiency of babies induced by dicumarol in mothers' milk cannot be considered wholly settled, although prothrombin deficiency did not occur in our two cases. When dicumarol is given to a mother who is nursing a baby, it is probably the course of wisdom to give the baby vitamin K or to determine values for prothrombin in the baby's blood and to correct any deficiency of prothrombin which may occur.

### EXPERIENCE WITH MEDICAL PATIENTS

A group of 288 patients who had various kinds of vascular diseases have been given dicumarol as part of their program of medical treatment. A



summary of the diseases from which these patients were suffering and the results of anticoagulant treatment is given in table 4.

The three large groups consisting of those who had thrombophlebitis, pulmonary embolism or acute arterial occlusion are worthy of more detailed consideration.

TABLE IV  
Results of Treatment of 288 Medical Patients with Dicumarol

Condition Treated with Dicumarol	Total Patients Treated	Subsequent Fatal Pulmonary Embolism	Subsequent Nonfatal Pulmonary Embolism	Subsequent Venous Thrombosis
Thrombophlebitis	138	0	2	4
Pulmonary embolism	44	0	1	0
Sudden arterial occlusion	45	0	0	0
Thrombo-angiitis obliterans	23	0	0	0
Arteriosclerosis obliterans	17	0	0	0
Miscellaneous*	21	0	0	0
Totals	288	0	3	4

\* Includes patients who had chronic venous insufficiency, congestive heart failure, simple arterial thrombosis, cerebral thrombosis and other diseases.

*Thrombophlebitis.* In this group were 138 patients. The thrombophlebitis was of the idiopathic type (one episode) in 42 cases and of the recurrent idiopathic type (several episodes) in 27. In 16 cases the thrombophlebitis followed trauma, in eight it was associated with acute infections, in eight with carcinoma, in five with blood dyscrasias, in four with thrombo-angiitis obliterans and in 11 with miscellaneous conditions which may cause thrombophlebitis. In 17 cases the thrombophlebitis occurred in varices including incompetent greater and lesser saphenous systems.

In 90 cases the thrombophlebitis involved the iliofemoral or deep sural veins or both.

The chief reason for giving dicumarol was to prevent pulmonary embolism and further venous thrombosis. There is no reliable information available as to the incidence of subsequent pulmonary embolism or venous thrombosis among patients who have thrombophlebitis which does not follow operation but it is reasonable to assume that it may be about as high as in the group of patients who have iliofemoral or sural thrombophlebitis following operations.

In this group fatal pulmonary embolism did not occur; two patients had nonfatal pulmonary embolism during adequate prothrombin deficiency. In four cases subsequent venous thrombosis developed. In one of these cases it occurred after the administration of dicumarol had been discontinued because of difficulties in obtaining blood for prothrombin determinations and after the prothrombin value had returned to normal; in another the venous thrombosis occurred when the prothrombin value was greater than 30 per

cent. In the two remaining cases there was adequate prothrombin deficiency at the time of the development of the venous thrombosis.

*Pulmonary Embolism.* There were 44 patients in this group. The incidence of subsequent pulmonary embolism and venous thrombosis without anticoagulant therapy among medical patients who have iliofemoral or sural thrombophlebitis is unknown but it probably is the same as that noted among patients after operation.<sup>6</sup> In the group of medical patients with pulmonary embolism now being considered, who were treated with dicumarol, there was no subsequent fatal pulmonary embolism or venous thrombosis; one patient had another nonfatal pulmonary embolism when the prothrombin value was between 20 and 30 per cent.

*Acute Arterial Occlusion.* A more detailed report of our experience with the use of anticoagulants in the treatment of acute arterial occlusion has been given elsewhere. The results of the use of anticoagulants in the treatment of 15 of the 45 patients on whom we are reporting data were recorded in that report.<sup>17</sup>

We have treated, now, acute arterial embolism in 19 cases and acute arterial thrombosis in 26 cases with anticoagulants. The plan of treatment has included the use of dicumarol with a period of preliminary heparinization. The patients have been divided into two groups: those whose treatment was instituted early (within 24 hours) and those whose treatment could not be started until more than 24 hours had elapsed from the time of the occlusion. In the group of 11 cases of acute arterial embolism in which treatment was started early, there was survival of the extremity in 10 (91 per cent). In the group of eight cases in which treatment was late, the extremity survived in only two (25 per cent).

In the group of 16 cases of acute arterial thrombosis with early treatment, the extremity survived in 13 (81 per cent) whereas in 10 cases with late treatment the extremity survived in five (50 per cent). These data indicate that when anticoagulant therapy is used in conjunction with other methods of emergency treatment one may expect survival of the extremity in a large number of cases if the treatment is started soon after the occlusion has occurred.

*Incidence of Bleeding in 288 Medical Cases.* Two patients bled from the gastrointestinal tract and one had severe subcutaneous bleeding. Treatment was discontinued in all instances. All patients recovered. Minor bleeding (epistaxis, hematuria and petechiae) occurred twice. Treatment was continued in all instances. The incidence of bleeding (1.0 per cent for major bleeding and 0.66 per cent for minor bleeding) was markedly less than the incidence noted in the postoperative cases considered earlier in this presentation.

*Duration of Administration of Dicumarol.* The use of dicumarol in a group of patients with occlusive arterial disease who required treatment over a long period gave us the opportunity to observe the effect of prolonged administration of dicumarol in a small group. In 41 cases dicumarol was

given for as long as one month, in 25 for two months, in nine for three months, in three for six months and in one for 10 months. No conclusion could be reached relative to the effectiveness of anticoagulants in the chronic occlusive arterial diseases. No untoward effects which might have resulted from the prolonged administration of the drug were observed in any of the cases. The prothrombin activity returned to normal in all within a few days after the administration of the drug was discontinued.

### CONCLUSIONS FROM EXPERIENCE WITH MEDICAL PATIENTS

Our experiences indicate clearly that the anticoagulants are effective in the treatment and prevention of vascular thrombosis of medical patients just as they are effective in the care of postoperative patients with these conditions. Fatal pulmonary embolism can be prevented and venous and arterial thrombosis can be halted in most instances. Early treatment of sudden arterial occlusion with anticoagulants and other measures results in survival of the extremity in 90 per cent of instances of embolism and 80 per cent of instances of thrombosis.

### SUMMARY

1. The expert use of the anticoagulants, heparin and dicumarol, has improved tremendously the outlook for patients who have acute vascular thrombosis.

2. An over-all consideration of 1,513 postoperative patients treated with anticoagulants indicates that the following results were achieved: 85 patients survived who would have been expected to die from pulmonary embolism; 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism.

3. A consideration of 288 medical patients indicates that fatal pulmonary embolism was prevented by anticoagulants. Nonfatal pulmonary embolism and venous thrombosis occurred very infrequently.

4. A study of 50 cases of acute myocardial infarction indicates substantial reduction in the incidence of further myocardial infarction and in arterial embolism and venous thrombosis.

5. Survival of the extremity occurred in 91 per cent of cases of arterial embolism and in 81 per cent of cases of arterial thrombosis, if treatment with anticoagulants was begun early and supplemented by other treatment.

6. In general, the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism.

## BIBLIOGRAPHY

1. BUTT, H. R., ALLEN, E. V., and BOLLMAN, J. L.: A preparation from spoiled sweet clover [3,3'-methylene-bis-(4-hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood: preliminary report of experimental and clinical studies, *Proc. Staff Meet., Mayo Clin.*, 1941, xvi, 388-395.
2. ALLEN, E. V.: The clinical use of anticoagulants. Report of treatment with dicumarol in 1,686 postoperative cases, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 323-329.
3. BARKER, N. W.: Anticoagulant therapy in postoperative thrombophlebitis and pulmonary embolism, *Minnesota Med.*, 1946, xxix, 778-782.
4. LINK, K. P.: The anticoagulant from spoiled sweet clover hay. In *The Harvey Lectures*, The Science Press Printing Company, Lancaster, Pennsylvania, 1943-1944, xxxix, 162-216.
5. HURN, MARGARET, BARKER, N. W., and MAGATH, T. B.: Determination of prothrombin time following administration of dicumarol, 3,3'-methylenebis (4-hydroxycoumarin), with special reference to thromboplastin, *Jr. Lab. and Clin. Med.*, 1945, xxx, 432-447.
6. BARKER, N. W., NYGAARD, K. K., WALTERS, WALTMAN, and PRIESTLEY, J. T.: A statistical study of postoperative venous thrombosis and pulmonary embolism. I. Incidence in various types of operations, *Proc. Staff Meet., Mayo Clin.*, 1940, xv, 769-773.
7. BARKER, N. W., NYGAARD, K. K., WALTERS, WALTMAN, and PRIESTLEY, J. T.: A statistical study of postoperative venous thrombosis and pulmonary embolism. IV. Location of thrombosis: relation of thrombosis and embolism, *Proc. Staff Meet., Mayo Clin.*, 1941, xvi, 33-37.
8. NICHOL, E. S., and PAGE, S. W., JR.: Dicumarol therapy in acute coronary thrombosis; results in fifty attacks, with review of data on embolic complications and immediate mortality in myocardial infarction, *Jr. Florida Med. Assoc.*, 1946, xxxii, 365-370.
9. PETERS, H. R., GUYTHER, J. R., and BRAMBEL, C. E.: Dicumarol in acute coronary thrombosis, *Jr. Am. Med. Assoc.*, 1946, cxxx, 398-403.
10. WRIGHT, I. S.: Experiences with dicumarol (3,3'-methylene-bis-[4-hydroxycoumarin]), in the treatment of coronary thrombosis with myocardial infarction; preliminary report, *Am. Heart Jr.*, 1946, xxxii, 20-31.
11. PARKER, R. L., and BARKER, N. W.: The treatment of acute myocardial infarction with anticoagulants, *Proc. Staff Meet., Mayo Clin.*, 1947, xxii, 185-192.
12. NAY, R. M., and BARNES, A. R.: Incidence of embolic or thrombotic processes during immediate convalescence from acute myocardial infarction, *Am. Heart Jr.*, 1945, xxx, 65-76.
13. DAVIS, ALBERT, and PORTER, MARGARET: Dicoumarin in the treatment of puerperal thrombosis, *Brit. Med. Jr.*, 1944, i, 718-719.
14. BARNES, A. C., and ERVIN, H. K.: The effect of the anticoagulants on postpartum bleeding, *Surg., Gynec. and Obst.*, 1946, lxxxiii, 528-530.
15. QUICK, A. J.: Experimentally induced changes in the prothrombin level of the blood. III. Prothrombin concentration of new-born pups of a mother given dicumarol before parturition, *Jr. Biol. Chem.*, 1946, clxiv, 371-376.
16. FIELD, J. B.: Hypoprothrombinemia induced in suckling rats by feeding 3,3'-methylenebis (4-hydroxycoumarin) and acetylsalicylic acid to their mothers, *Am. Jr. Physiol.*, 1945, cxliii, 238-242.
17. BARKER, N. W., HINES, E. A., JR., and KVALE, W. F.: The treatment of acute arterial occlusion of the extremities with special reference to anticoagulant therapy, *Minnesota Med.*, 1946, xxix, 250-252; 280.

## SOME OBSERVATIONS ON BLEEDING TENDENCY IN THROMBOCYTOPENIC PURPURA \*

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IN a previous communication it was reported that in irradiation hemorrhage (roentgen-ray) an anticoagulant was present in the blood.<sup>1</sup> This anticoagulant was indistinguishable from heparin. The hemorrhagic tendency in dogs could be prevented or stopped temporarily by the intravenous injection of protamine sulfate or toluidine blue. Both of these substances are capable of binding heparin and rendering it biologically inactive so far as its anticoagulant properties are concerned. They do not appear to affect any other phase of the clotting mechanism except to act as anticoagulants when present in excess.<sup>1</sup> These agents were effective even in the face of marked thrombocytopenia and did not alter the platelet count in these animals.

Total body irradiation is characterized by severe thrombocytopenia, a prolonged bleeding time and a prolonged clotting time. Aside from the prolonged clotting time, the hemorrhagic characteristics of this disease are similar to those of thrombocytopenic purpura in man, whether primary or secondary. The marrow picture in these disorders may vary from one of hyperplasia to complete aplasia, depending upon the marrow defect. Inasmuch as the thrombocytopenia, the prolonged bleeding time and the petechial hemorrhages appeared common to all of these disorders, it was decided to determine the heparin tolerance of normal and thrombocytopenic patients' bloods, and to establish what, if any, effect toluidine blue or protamine had upon the hemorrhagic tendency.

This report is primarily concerned with the results obtained from the intravenous administration of toluidine blue upon the hemorrhagic manifestations of thrombocytopenia. Attempts were made, however, to determine the effect of increasing amounts of heparin upon the whole blood clotting time of purpuric patients with thrombocytopenia. Similar control studies were made upon three to five normal bloods each time the thrombocytopenic patients were tested. In each case a series of 10 serology tubes were placed in a rack and to each was added small increasing amounts of protamine sulfate dissolved in normal saline. Blood was drawn from the antecubital vein into dry 10 c.c. syringes. This blood was then placed in a dry test tube. Eight c.c. were then rapidly pipetted into a second test tube

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containing 0.2 mg. of heparin (liquid). After gently mixing, 0.8 c.c. of blood was placed in each of 10 tubes, each of which contained increasing amounts of liquid protamine sulfate (0.00 mg. to 0.36 mg.). Micropipettes were used for both the heparin and protamine measurements, and in both cases the same stock solutions were used for the controls and the thrombocytopenic bloods. There was evidence that both the heparin and protamine solutions slowly deteriorated, but since these changes affected both the test and normal bloods, these changes did not appear to alter the clotting time relationships.

An example of the increased susceptibility of thrombocytopenic blood to heparin is demonstrated in figure 1. It will be noted that more protamine sulfate was necessary to restore the normal clotting time in the thrombocytopenic blood than was required by normal controls. This procedure was carried out daily for five days before toluidine blue was given. The clotting curves all followed similar patterns. The patient, suffering from idiopathic thrombocytopenic purpura whose blood had been thus tested, was then given dye (2.5 mg. per kg. of body weight). The following morning she was free from bleeding and no new petechiae had appeared. According to the patient she was free from oral bleeding for the first time in eight months. Twenty-four hours after the injection of toluidine blue her blood was again titrated for heparin tolerance. The results are also charted in figure 1. It will be noted that less protamine was necessary to restore normal clotting time than was required before the dye was injected. Not shown in this chart are data obtained the day following the second dye injection (1.5 mg. per kg. of body weight) when the heparin tolerance was entirely restored to normal.

A more extensive report upon this phase of the problem will be reported elsewhere.

Reported below is our clinical experience with toluidine blue administration as a means of aiding in the control of petechial hemorrhages in thrombocytopenia. This report is limited in experience and is comprised of six cases. Four of these were thrombocytopenic purpura associated with acute or subacute leukemia. Two were idiopathic thrombocytopenic purpuras. Two other cases were treated with favorable results but data were insufficient to justify inclusion here. The preliminary nature of this report is emphasized.

#### CASE REPORTS

*Case 1.* L., a female, age 49, complained of malaise and increasing weakness of two months' duration. Three weeks before admission ecchymoses were first noted. Ten days later she was admitted to another hospital where a diagnosis of acute myelogenous leukemia was made. Her platelet count was 23,000 and the bleeding time was prolonged to more than an hour. She was given five transfusions during the next five days along with vitamin K, vitamin C, rutin and calcium gluconate. The bleeding persisted and became so marked that it was necessary for her to carry a basin constantly under her chin. There were, however, no oral ulcerations and the gums were not swollen when she was transferred to the Billings Memorial Hospital. The prothrombin time and whole blood clotting times were normal. The platelet

## HEPARIN-PROTAMINE TITRATION IN THROMBOCYTOPEAIC-PURPURA

♀-AGE 41-C

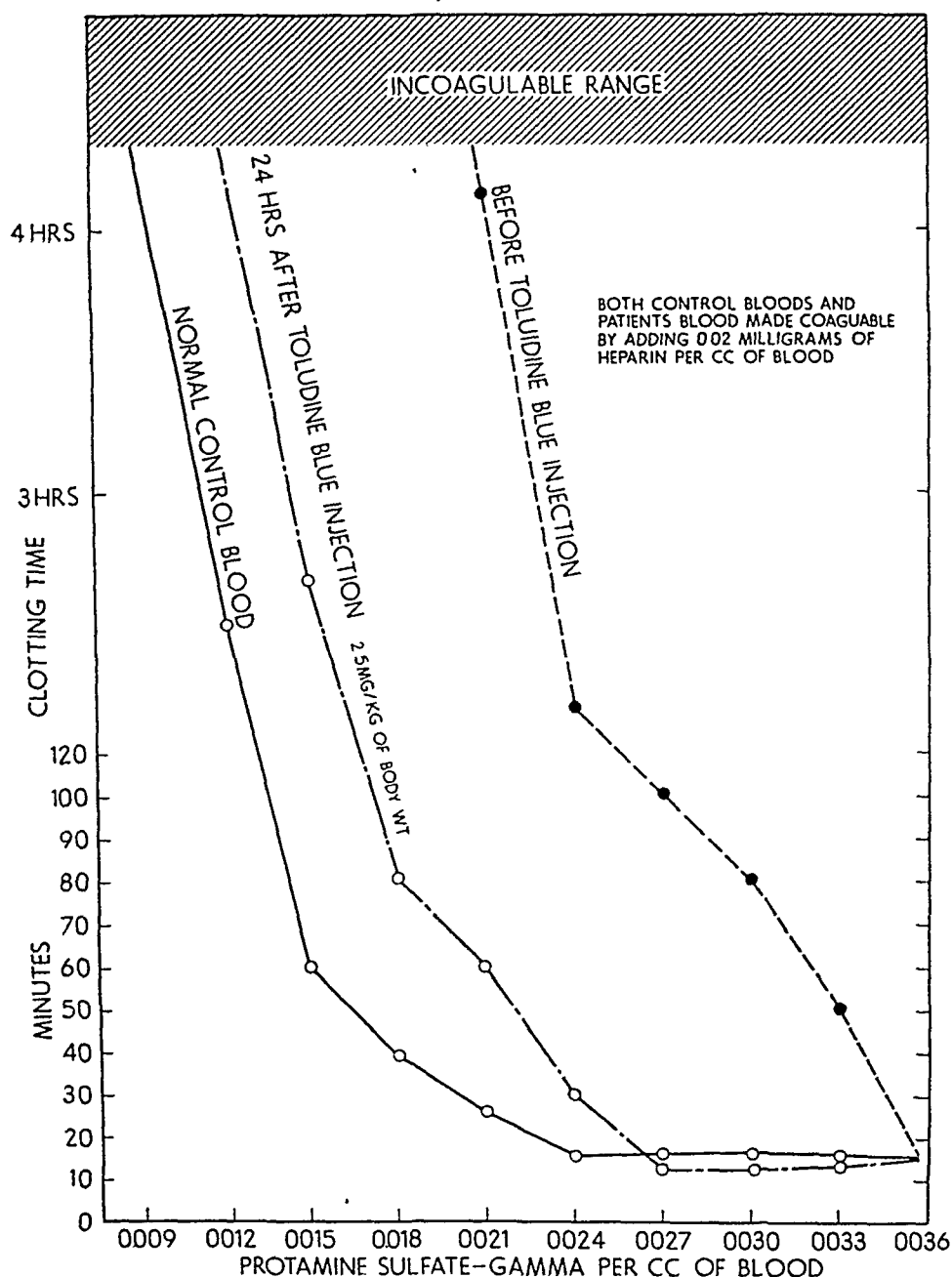


FIG. 1. In this chart is shown the amount of protamine sulfate required to restore the normal clotting time of whole blood made incoagulable by the in vitro addition of standard amounts of heparin. Twenty-four gamma of protamine were necessary to restore to normal the clotting time of normal blood, while 36 gamma were required to restore normal clotting time in the untreated thrombocytopenic patient (curve on far right). Twenty-four hours after toluidine blue injection the amount of protamine necessary to restore normal clotting time in this patient was 27 gamma per c.c. (see text).

count varied between 20,000 and 60,000 and the bleeding time was continually longer than one hour. The diagnosis of acute myelogenous leukemia was confirmed by sternal puncture from which she bled for two days. In view of the failure of other measures to control hemorrhage, she was given 2 mg. of toluidine blue in saline per kilo of body weight 12 hours after admission. The bleeding stopped within eight to 10 hours. A second dose of 1.5 mg. of dye per kg. of body weight was given the following day. The bleeding time was not shortened, but her petechiae began to resorb and no new ones appeared. Three days later oral bleeding again appeared at which time the original 2.0 mg. dose of dye was repeated. Bleeding stopped within 20 minutes but again the bleeding time was not shortened. Two days later oral bleeding again appeared. A photograph of her mouth at this time was taken (figure 2 a).

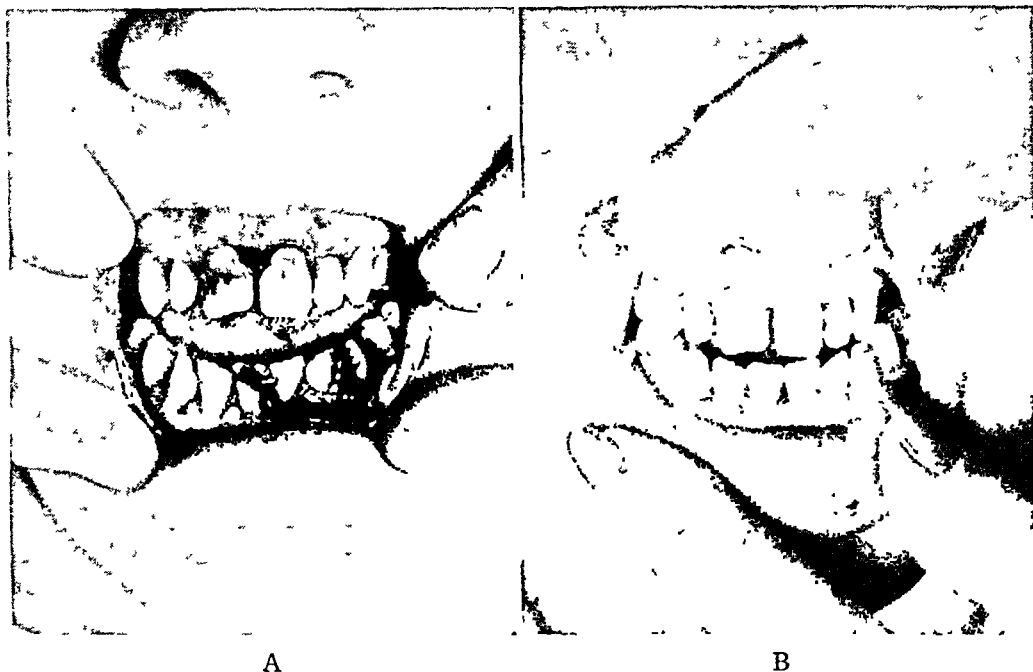


FIG. 2. Two photographs of the mouth of a patient (Case 1) suffering from spontaneous oral bleeding from thrombocytopenia secondary to acute myelogenous leukemia. These pictures were made just before (a) and 12 hours after (b) the patient received toluidine blue intravenously. Observe the absence of oral ulcerations. Though the bleeding was controlled, the bleeding time was not shortened.

She vomited 400 c.c. of fresh blood. Three mg. of dye per kg. of body weight was given at this time and again all evidence of bleeding ceased within 20 to 30 minutes. The second photograph (figure 2 b) was taken 12 hours later. The patient was not allowed to wash her mouth for three hours before either photograph was made. Clinically the patient was improved and felt better when hemorrhage was absent. However, it did not affect the character of her primary disease, and she died seven days after her last dye injection.

*Case 2.* A 2½ year old female child was admitted from another hospital because of uncontrollable bleeding and tracheal compression from mediastinal and cervical nodes. A diagnosis of subacute leukemia was made five months before her admission to the Bobs Roberts Hospital. On admission to this hospital a diagnosis of monocytic leukemia was established. Enlarged lymph nodes, spleen and liver were observed. Oral ulcerations were present from which blood continued slowly to ooze. The platelet count ranged between 15,000 and 23,000. Because her condition ap-



peared terminal in spite of conservative measures and because her bleeding was not controlled by transfusions, vitamin K, or vitamin C, she was given 3 mg. of toluidine blue per kilo of body weight intravenously in 300 c.c. of normal saline. Seven of the nine subsequent days she received 2 mg. doses of the dye per kg. of body weight. Photographs of her mouth and forearms were taken before and after dye was injected (figure 3). The oozing about her mouth stopped after a few hours and no new petechiae appeared. The ulcerations about the gums began to heal. The clots formed scabs which were undermined with new epithelium. Subsequent photographs are shown which were taken during this process of repair. While the oozing abruptly stopped, nearly 10 days elapsed before the gums and lips were reëpithelialized. As in Case 1, the bleeding time was not shortened and the platelet count remained constantly below 50,000. This patient received some palliation but the ultimate course of her disease was not altered. She died two weeks after her last dye injection. The control of hemorrhage by the administration of dye, however, was striking. Within three days after the initial administration of the dye the petechiae had all disappeared (figure 4). Many ecchymotic areas continued to re-appear at the sites of needle puncture, but none appeared spontaneously or in the absence of trauma.

*Case 3.* An eight year old boy was admitted to the hospital with a diagnosis of subacute myelogenous leukemia of eight months' duration. He had received fresh whole blood transfusions on January 30, and February 2, 3, and 4, 1947. In spite of these measures, he developed gross hematuria and eye ground hemorrhages. Hence on February 5, 4 mg. of toluidine blue per kilo of body weight were administered by slow intravenous drip. Eight hours later the urine contained only 8 to 12 red cells per high power field. By the following day all evidence of bleeding had ceased. No new hemorrhages in the eye grounds appeared, and the old ones resorbed. The bleeding time continued prolonged and the platelet count remained below 50,000. Two days after the dye injection the child suffered a severe nasal hemorrhage at the site of an old intranasal ulceration which previously had bled. A freshly drawn 500 c.c. blood transfusion was given. The bleeding promptly stopped and the bleeding time dropped from 55 minutes to seven minutes.

In this case the tendency for spontaneous hemorrhage ceased after the administration of dye. As in Cases 1 and 2 the bleeding time was not shortened until a large fresh whole blood transfusion was given. Presumably the platelet count was sufficiently elevated to enable a normal platelet thrombus to form, thus shortening the bleeding time.

*Case 4.* A 45 year old male with subacute myelogenous leukemia known to be present for five months, became severely anemic and his platelet count fell to less than 50,000. Petechiae appeared over the lower extremities and oral bleeding occurred. Oral ulcerations were present and the gingival margins became edematous. The bleeding time exceeded 50 minutes on three occasions. He was given 2.0 mg. per kg. of body weight of toluidine blue; and 1.0 mg. per kg. the following day. No new petechial hemorrhages appeared and oral bleeding from the ulcerated areas was markedly reduced but not completely controlled. Twenty-four hours later a freshly drawn citrated whole blood transfusion was administered following which all evidence

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FIG. 3. This is a series of four photographs made over a 12 day period of the oral bleeding of a 2½ year old child suffering from subacute monocytic leukemia and secondary thrombocytopenia. Oral ulcerations were numerous about the lips as shown in photographs A and B. Toluidine blue was administered seven out of nine days (see text, Case 2). Photograph A was made immediately before the initial injection, photograph B was made two days later after two doses of dye had been given. Note that nearly all the gingival ooze had ceased but that the encrusted blood about the lips persisted although somewhat diminished. Photograph C was made on the ninth day after the patient received the last (seventh) dose of toluidine blue. On the fourteenth day, five days after the last dye injection, spontaneous bleeding again recurred as shown in photograph D.

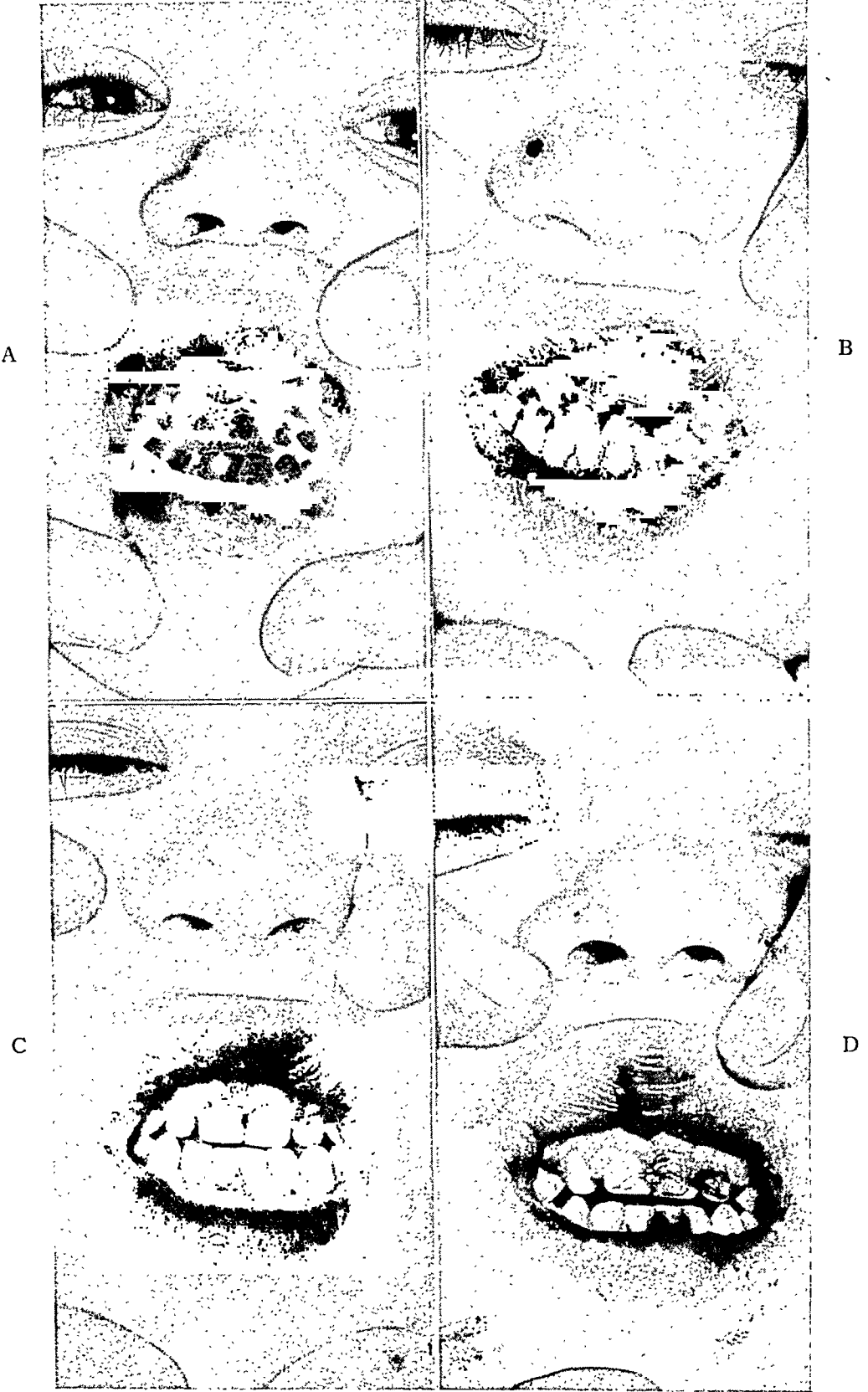


FIG. 3.

of bleeding promptly stopped. Transfusions given before dye injection had not altered the hemorrhagic tendency. As in Case 3, much of the bleeding appeared due to ulcerations which bled because the platelet count was low. Apparently the platelet thrombi were slowly formed and easily dislodged. This patient like Case 3 received maximum benefit when both blood and toluidine blue were given.

*Case 5.* A 22 year old female had a history of intermittent purpura of five years' duration. Splenectomy was performed when other methods failed to control bleeding. A prompt rise in the platelet count occurred. Six hours after splenectomy it was 420,000 per cu. mm. of blood. However, by the end of two weeks her platelet count was 140,000 and petechiae reappeared. At this time her bleeding time was 70 minutes. She was then given 2 mg. of toluidine blue in 500 c.c. of saline intravenously, and was kept ambulatory. No new petechiae appeared and the tourniquet test became negative. The bleeding time on this occasion was reduced to seven minutes. The platelet count continued to drop and reached 60,000 to 80,000 by the end of the third week even though splenectomy had been performed and all visible accessory splenic tissue had been removed. The bleeding time again became prolonged when the platelet count fell below 90,000, and at these low levels it was not shortened by the administration of the dye. New showers of petechial hemorrhages appeared when the dye was not administered. Transfusions, however, did not influence the formation of petechiae. Five weeks after splenectomy her menstrual period began. The flow was profuse and not relieved by transfusions or toluidine blue. However, she was not given the dye or blood together or on consecutive days. Hysterectomy was then performed and the patient made an uneventful recovery. Petechiae continued periodically and the thrombocytopenia and prolonged bleeding time were still present nine months after splenectomy.

This patient is also of interest in that she was successfully delivered six months before splenectomy even though she suffered from marked thrombocytopenia (60,000) at that time. The infant at birth had a platelet count of 40,000 which, after three weeks, began to return to normal. It has remained normal for over one year. This finding argues strongly in favor of a circulating substance which is transmissible across the placental barrier and which then is capable of reducing the platelet numbers of the fetus.

*Case 6* was a 41 year old female with idiopathic thrombocytopenic purpura who suffered from oral bleeding for eight months without remission. No drug or allergic history could be elicited. Repeated studies of the platelet count, bleeding and clotting times, sternal marrow studies, and the absence of other disease confirmed our diagnosis. Photographs of her lower extremities were taken before therapy was begun (figure 5 a). After a five day study period she was given toluidine blue (2.5 mg. per kg. of body weight). The following morning she was free from oral bleeding for the first time in eight months. No new petechiae could be seen, her platelet count remained at 60,000 and her bleeding time continued prolonged. On the third day photographs again were taken (figure 5 b) which showed some remission of her petechiae. The next day bleeding again occurred and new showers of petechiae appeared. The same dose of dye was again given with similar results. Four days later the dye was again given even though the patient was not bleeding. Splenectomy was refused and the patient was discharged. She was given toluidine blue in capsules to be taken orally. Each capsule contained 150 mg. of dye. The oral dye proved ineffective as it had in dogs.<sup>1</sup> She reported that she had taken one capsule daily but that on the fifth day heavy petechial showers appeared over the lower extremities and her oral bleeding returned. On this day she was seen in the Out Patient Department where 2.5 mg. of dye per kg. of body weight were given intravenously. Her bleeding stopped and no new petechiae appeared. She was readmitted to the hospital three days later and given two fresh whole blood transfusions daily for three days. After



A

B

FIG. 4. Photograph A shows many petechiae of the right forearm of Case 2 before dye injection. Photograph B, taken on the ninth day, shows no petechiae although many ecchymoses are present at the sites of vena punctures and penicillin injections. The bleeding time was not shortened.

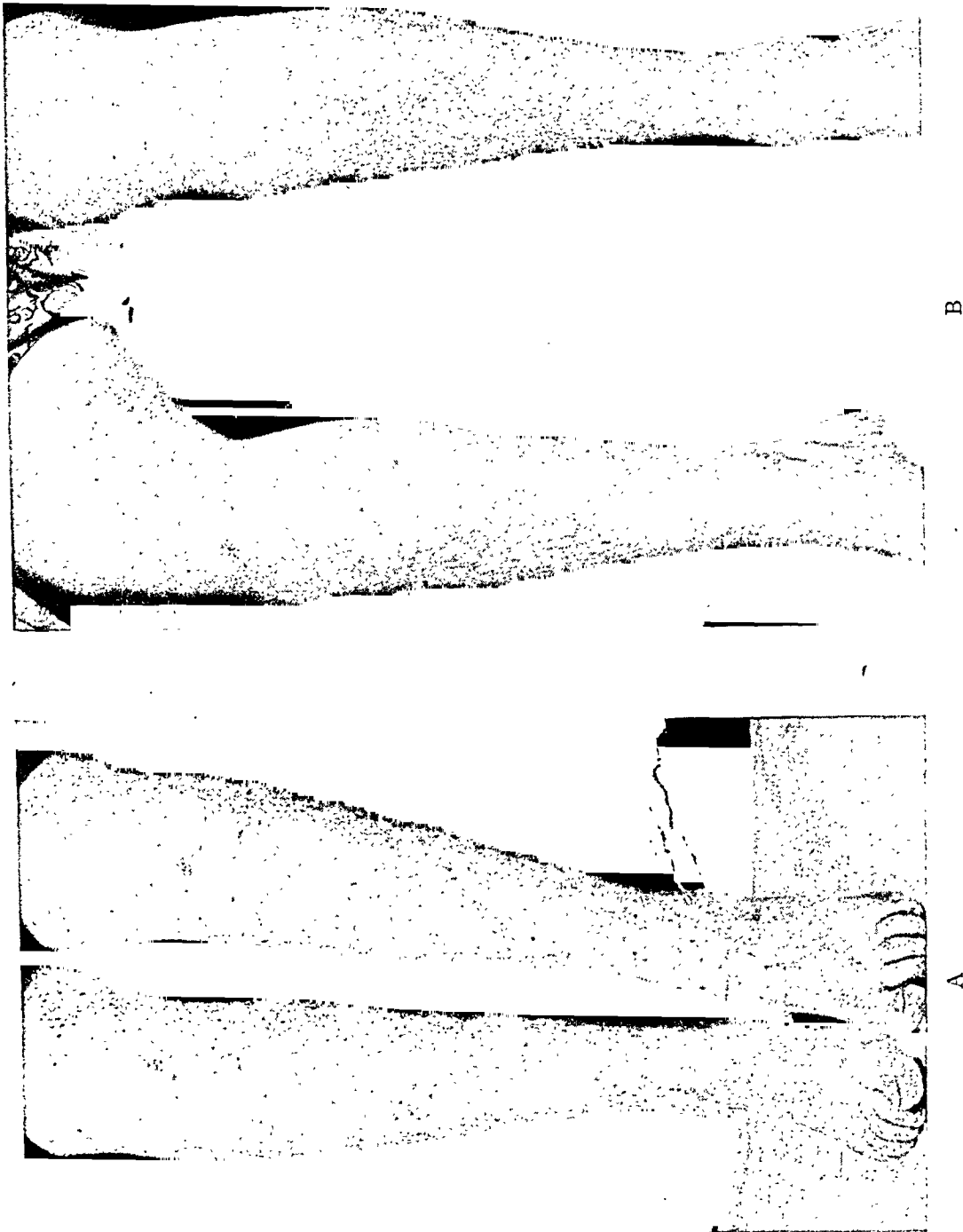


FIG. 5. Photographs A and B of Case 6 were taken before (a) and three days after (b) a single injection of toluidine blue. A decrease in the number of petechiae is apparent. On the following day new showers of petechiae appeared but these were again controlled by the injection of the dye. The bleeding time was not shortened.

the second transfusion bleeding recurred and continued in spite of four more transfusions (500 c.c. each). The patient refused further therapy and died on the ninth hospital day from intracranial hemorrhage. Autopsy was not permitted.

## DISCUSSION

Thrombocytopenia is found in a number of blood disorders. Some of these disorders appear to be distinctly different and probably unrelated. For example severe thrombocytopenia may occur in pernicious anemia, aplastic anemia, and leukemia. Hemorrhage may appear in all three of these syndromes, but it is not regularly present in any one. Bleeding probably presents a greater problem in the acute leukemias than in aplastic anemia or pernicious anemia. In the latter it is apparently comparatively rare even though the thrombocytopenia may be severe.<sup>2</sup> These features do not argue for a similarity in the primary disease, but they do emphasize the need for a better knowledge of platelet physiology.

The importance of the platelet in the normal hemostatic mechanism is well established, although there has been some difference of opinion as to how they function in this respect. All are agreed that platelets rapidly agglutinate at the site of endothelial injury, and that the size of the platelet thrombus depends upon the number which flow past the traumatized area. In the smaller vessels (capillaries and venules) the platelet thrombus may be the only hemostatic mechanism necessary to control bleeding. In the larger vessels, fibrin formation plays the more important rôle and rapidly makes its appearance soon after the platelet thrombus begins to form.

The "sticky" or adhesive quality of platelets is well known. It is an important factor in causing the platelet to adhere and agglutinate at the site of vascular injury. Fibrin is deposited and becomes enmeshed in the platelet thrombus which normally holds fibrin at the site of injury. When platelets are absent or reduced in number, the clots are friable and easily dislodged; hence in thrombocytopenia, clots form but they may be subsequently washed away and give rise to further hemorrhage.

Clot retraction or syneresis is greatly influenced by the platelet number. It may be absent or long delayed in thrombocytopenia. Syneresis is a function of the intact platelet as extracts of platelets are inactive in this respect.<sup>3</sup> As the clot retracts the rent in the vascular wall is partially or completely occluded and in this manner syneresis contributes to hemostasis.

Platelets are rich in cephalin and lipoproteins and are thromboplastic. A good portion of the platelet thrombus undergoes lysis, liberating thromboplastin. These thromboplastic substances are so generously contained in almost all body tissues that it seems unlikely that any diminution in platelet number should greatly alter the amount of thromboplastin available for clotting. The fact that the clotting time is normal in thrombocytopenia is evidence that an adequate amount of thromboplastin is available from other sources (erythrocyte, leukocyte, platelet, and surrounding tissue).

The platelet thrombus is the result of platelet agglutination, platelet adhesiveness and clot retraction. The platelet thrombus is probably indispensable to the normal mammalian hemostatic mechanism *in vivo*. Other factors may contribute to *in vivo* clotting but of those known, the formation of the normal platelet thrombus and the fibrin clot are most important. The platelet thrombus is the first observable response to vascular injury and in some cases it may be the only response. A deficiency in the platelet number retards the formation of the platelet thrombus and probably accounts for the prolonged bleeding time in thrombocytopenic purpura. The reduced platelet number impairs clot retraction and adhesiveness, resulting in friable, bulky and easily dislodged clots. These deficiencies probably account for the prolonged bleeding time in thrombocytopenia.

What can not be explained on the basis of thrombocytopenia is capillary fragility. It is possible that the platelets are normally concerned with the preservation of capillary integrity in some way not yet known. It has been suggested that they are normally concerned with "plugging" fenestra in capillary walls, although no evidence has been produced to show that such a phenomenon ever occurs. It is more likely that the increased capillary fragility is the result of other disturbances which accompany the appearance of thrombocytopenia. The disturbed capillary integrity in thrombocytopenic purpura may return to normal even though thrombocytopenia may persist, although usually these two phenomena coincide.<sup>4</sup>

The capillary factor is demonstrated by methods which either increased the intracapillary pressure (venous constriction) or by methods which lessen the extracapillary pressure (negative pressure). Because of the increased capillary permeability in thrombocytopenic purpura, the petechiae are gravitational in their distribution. The gravitational character of petechiae serves to emphasize the importance of the capillary defect and makes difficult an explanation of petechiae on the basis of thrombocytopenia alone.<sup>5</sup> In severe cases petechiae may appear even without gravitational influence although they are usually more numerous in the dependent portions of the body.

The importance of the capillary factor is demonstrated by the patient with thrombocytopenia but with remission of petechiae.<sup>3, 4, 5</sup> In such patients internal bleeding is not a serious problem, yet when spontaneous petechiae reappear the critical character of the disease is again apparent.

Successful treatment then must be directed at both the capillary defect and at restoring the platelet number. It is likely that a common agent is responsible for both defects and that its elimination would result in a cure of the disease. Thus far, no such factor has been identified, although in allergic purpuras relief from hemorrhage occurs as the allergic state subsides. Unless one concludes that the disease known as Werlhoff's disease is in reality an unidentified allergic state some other primary disturbance must be assumed. Until the primary disorder has been recognized, treatment must

be directed so as to correct both thrombocytopenia and the increased capillary permeability.

Some degree of palliation results from blood and plasma transfusions. The rise in platelet number is slight to moderate and may be enough to temporarily shorten the bleeding time (Case 5). There is some evidence that the plasma may contain some substance or group of substances capable of correcting petechiae in the less severe cases. However, it is because of the failure of this type of supportive measure that the use of splenectomy in the treatment of idiopathic thrombocytopenic purpura has persisted. Just why splenectomy should prove beneficial has never been clearly understood. The rise in the platelet number after splenectomy in Werlhoff's disease is often spectacular, but similar sharp rises in the platelet count (over one million) have been observed in patients where splenectomy is performed incidental to other surgical disease (carcinoma of the stomach).<sup>6</sup> It appears likely that the removal of the normal spleen in man permits thrombocytosis, and because of this fact splenectomy affords a convenient method of elevating the platelet count in idiopathic thrombocytopenic purpura. However, in secondary thrombocytopenia, splenectomy may be ineffective<sup>5,7</sup> and its failure not understood.

In severe bleeding any measure that can aid in elevating the platelet count should be used. The hazards of impaired platelet thrombi formation and poor clot retraction have been discussed. Blood transfusions should always be used, especially in the postoperative patient with recurrence of thrombocytopenia and bleeding.

Our own limited experience with the use of antiheparin toluidine blue and back titrations of heparinized blood, suggests that in thrombocytopenia, an increased amount of heparin-like substance may be present in the blood. These patients appear to be improved; generalized oozing stops *except from ulcerated areas* when toluidine blue or protamine sulfate are given. The bleeding time is *not* shortened, but petechiae are held in check. If the ulcerated areas are allowed to crust over so that scales form, these may heal if the general tendency to ooze is controlled by frequent administration of blood transfusions and antiheparins.

The continued and joint administration of toluidine blue and blood to correct capillary defect and to restore the platelet thrombi formation to near normal appears to be more effective than either alone. The dye appears to be concerned more with the capillary disturbance than with the impaired platelet thrombi formation. The latter can only be corrected by the administration of fresh blood or plasma.

Toluidine blue or protamine are fairly well tolerated when given intravenously in man. We have administered the dye dissolved in 250 to 500 c.c. of normal saline. The dosage of each has ranged from 1 mg. to 4 mg. per kg. of body weight. The dye-saline or protamine-saline mixture were administered intravenously over a two hour period. An initial dose of about



2.5 mg. of either substance per kg. of body weight proved satisfactory. Each day thereafter 1.5 to 2.0 mg. was given until all oozing stopped and new petechiae no longer appeared. Usually 24 to 48 hours (or two to three doses) were sufficient. Thereafter 1.5 to 2.5 mg. per kg. dose was administered every second, third or fourth day or as bleeding recurred. Again, it cannot be overemphasized that while bleeding from oral or cutaneous ulcer may be lessened after dye or protamine administration, they usually will not entirely cease unless the platelet count is partially elevated by transfusions. When such bleeding persists after the appropriate administration of toluidine blue, fresh whole blood transfusions should be given.

Little is known of the toxicity of toluidine blue. In normal dogs we found it to be strongly hemolytic. Leukocytosis and thrombocytosis also occurred.<sup>6</sup> However, methylene blue, a closely related compound chemically, and known to be of low toxicity in man, was as toxic as toluidine blue when given intravenously to dogs at similar dosage levels. In man we have not seen this type of reaction within the dosage levels used. In fact, aside from apprehensiveness in two patients on one occasion each, no untoward effects were noted. Apparently the dye is excreted in the urine and into the intestinal tract as both the urine and the stool become highly colored. After a single dose of approximately 2.0 to 2.5 mg. per kg. of body weight the urine and stool remained colored for 36 to 48 hours. Most of the dye is excreted by the end of 24 hours, and in the doses that we used the patient's skin was not discolored. It remains to be seen whether patients receiving the dye shortly before death may not be discolored when embalmed as in the case when methylene blue has been given premortally.

Toluidine blue is not active when given orally to either dog or man within the range from 1 to 5.0 mg. per kg. of body weight. Its failure orally is probably due to absorption of dye by the mucoproteins of the intestinal tract. Protamine sulfate is not active when given orally either, presumably because of digestion within the intestinal tract.

## SUMMARY

1. The effect of toluidine blue administered intravenously on petechial hemorrhage in patients with thrombocytopenic purpura is described.

2. Preliminary evidence is presented which suggests that the blood of thrombocytopenic patients tolerates heparin less well than does normal blood.

3. The dye appears to affect capillary permeability, aiding only in controlling petechiae. The bleeding time is not shortened and bleeding from ulcerated or denuded areas is not materially altered, unless whole blood transfusions are given or spontaneous platelet elevation occurs.

4. These observations are probably of greater physiologic interest than therapeutic value in these diseases.

5. The preliminary nature of these observations is emphasized.

## BIBLIOGRAPHY

1. ALLEN, J. G., and JACOBSON, L. O.: Hyperheparinemia: Cause of the hemorrhagic syndrome associated with total body exposure to ionizing radiation, *Science*, 1947, cv, 2728.
2. WINTROBE, M. N.: *Clinical hematology*, 1946, Lea and Febiger, Philadelphia.
3. TOCANTINS, L. M.: The mammalian blood platelet in health and disease, *Medicine*, 1938, xvii, 155-260.
4. BRILL and ROSENTHAL: Quoted by Tocantins, *ibid.*, 1938.
5. BOGARDUS, G., ALLEN, J. G., JACOBSON, L. O., and SPURR, C. L.: The rôle of splenectomy in thrombocytopenic purpura. In press.
6. Unpublished data, 1947.
7. ELLIOTT, R. H. E., JR.: A reëvaluation of splenectomy in thrombocytopenic purpura based on a 27 year combined clinic follow up experience, *Proc. Inst. Med. Chicago*, 1947, xvi, 330.
8. ALLEN, J. G., SANDERSON, M., MILHAM, M., KIRSCHON, A., and JACOBSON, L. O.: Hyperheparinemia and the hemorrhagic syndrome following total body exposure to ionizing radiation. In press, 1947.

# THE VALUE OF SPINAL FLUID EXAMINATION AS A DIAGNOSTIC PROCEDURE IN WEIL'S DISEASE\*

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It is well known that inflammation of the meninges may occur in Weil's disease, and that meningitis may occasionally be the principal clinical manifestation of that infection.<sup>1, 2, 3</sup> More commonly, however, meningeal involvement is evidenced only by abnormal changes in the spinal fluid. In cases observed recently at Grady Hospital, examination of the spinal fluid has revealed positive findings in Weil's disease with sufficient frequency to indicate that the procedure is of value as a diagnostic measure. This is important, in view of the fact that there is no satisfactory test for Weil's disease which is generally available or which gives a result quickly. The purpose of the present communication is to report the spinal fluid findings in our cases, together with similar information collected from the medical literature.

## INCIDENCE OF ABNORMAL SPINAL FLUID FINDINGS

The present series is comprised of 14 cases in adults, observed during the years 1943 to 1946. All had typical manifestations, including jaundice. The diagnoses were verified by agglutination test, muscle biopsy, or both. In six cases there were signs or symptoms suggesting the possibility of meningitis, such as nuchal rigidity, severe headache or convulsive seizures. The spinal fluid findings in this group of cases are listed in table 1. We have classified cell counts higher than 5 per cu. mm. as abnormal. It will be observed that in 13 of the 14 cases abnormal spinal fluid findings were noted at one or more examinations.

In a survey of the literature on Weil's disease, from 1916 until the present, comparable data were obtained on 83 cases. We did not include single case reports, or reports which did not give information regarding both positive and negative spinal fluid findings. The groups were unselected, except that patients with syphilis were excluded. As shown in table 2, spinal fluid abnormalities were found in 65, or 83 per cent, of 78 cases. When added to our 14 cases the total incidence is 78, or 86 per cent, of 92 cases. Clinical signs of meningitis were present in 41 per cent of cases in the combined series.

## TYPE OF SPINAL FLUID ABNORMALITY FOUND

Table 3 summarizes the spinal fluid abnormalities in a series of 97 patients, composed of the cases in table 2, together with five isolated case re-

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TABLE I  
Details of Spinal Fluid Findings in 14 Cases of Weil's Disease

Pt.	Day of Disease	Menin-geal Signs	Jaun-dice	Pressure (mm. sp. fl.)	Color	WBC's	Polys Per Cent	Lymphs Per Cent	Pandy	Protein (mg./100 c.c.)	Mastic
WKC	7th	+	+	110	0	5	50	50	Neg.	34	000000
	10th	0	0	—	0	0	—	—	—	—	—
HR	10th	+	+	Normal	Yellow	85	12	88	+	—	000000
MW	6th	0	+	Increased	Yellow	18	50	50	Tr.	54	111110
JV	12th	0	+	—	Yellow	27	37	63	+	75	000000
EH	14th	0	+	110	Yellow	17	0	100	Neg.	46	000000
DC	7th	0	+	—	0	46	40	60	+	28	000000
WBD	10th	0	+	130	Yellow	58	0	100	++	90	110000
	21st	0	0	140	0	9	0	100	Neg.	27	—
	37th	0	0	100	0	2	0	100	Neg.	27	000000
WP	11th	+	+	150	Yellow	65	0	100	Tr.	72	000000
CC	7th	0	+	—	Yellow	210	1	99	Neg.	74	000000
	14th	0	+	—	Yellow	95	1	99	Tr.	73	000000
JP	9th	0	+	146	Yellow	167	0	100	+	300	111100
	21st	0	+	170	0	5	20	80	+	45	—
JT	7th	+	+	170	Yellow	55	50	50	Neg.	72	000000
	17th	0	0	—	0	2	0	100	Neg.	—	—
NY	6th	+	+	340	Yellow	36	44	56	Neg.	49	000000
AC	5th	0	+	120	Yellow	38	0	100	Neg.	48	000000
	7th	0	+	—	Yellow	740	30	70	Neg.	—	—
	23rd	0	+	—	Yellow	0	—	—	Neg.	—	—
JES	8th	+	+	300	Yellow	147	41	59	—	134	—

TABLE II  
Incidence of Abnormal Spinal Fluid in Patients with Weil's Disease

Cases Reported by:	No. of Cases	No. with Abnormal Spinal Fluid	Per Cent with Abnormal Spinal Fluid	No. with Signs of Meningitis	Per Cent with Signs of Meningitis
Walch-Sorgdrager <sup>3</sup>	19	15	79	12	63
Costa and Troisier <sup>4</sup>	18	15	83	18	100
Clapper and Myers <sup>2</sup>	10	9	90	3	30
Ashe, et al. <sup>1</sup>	5	4	80	2	40
Minkenhof <sup>5</sup>	8	7	88	0 (?)	0
Cochez and Fichet <sup>6</sup>	3	2	67	3	100
Goldberg and Davens <sup>7</sup>	2	2	100	1	50
Garnier and Reilly <sup>8</sup>	11	11	100	3	27
Bruno, Wilen and Snively <sup>9</sup>	2	0	0	0	0
Cargill and Beeson	14	13	93	6	43
Total	92	78	86	38	41

ports from the literature.<sup>10, 11, 12, 13, 14</sup> The commonest positive finding was an increase in the number of cells. There was considerable variability in total count, the range being 6 to 3000 cells per cu. mm., although in most instances it did not exceed 100 per cu. mm. The peak of the elevation occurs between the fifth and ninth days of illness.

TABLE III  
Incidence of Individual Spinal Fluid Abnormalities

Abnormality	No. of Examinations	No. Abnormal	Per Cent Abnormal
Xanthochromia	29*	27	90
Increased cell count	97	84	87
Increased pressure	43	22	51
Positive Pandy	44	26	59
Increased protein	52	26	50
Positive mastic	18	4	22
Low sugar	35	1	3

\* Only jaundiced patients are included in this group.

TABLE IV

Day	Cell Count		Differential	
	No. of Cases	Average Cell Count	No. of Cases	Average Per Cent Lymphocytes
4th	3	11	2	68
5th	6	145	4	65
6th	11	128	10	61
7th	16	585	13	50
8th	8	383	6	30
9th	4	207	4	75
10th	7	74	7	85
11th	4	42	4	86
12th	2	215	1	41
13th	3	166	3	100
14th	3	65	3	93
15th	2	55	2	60
16th	1	6	0	—
19th	2	19	2	96
21st	3	9	3	93
22nd	1	9	1	100

The data on differential cell counts are summarized in table 4, where it will be seen that lymphocytes usually predominate, although during the first week of disease as many as 50 per cent of the cells may be polymorphonuclear leukocytes.

Xanthochromia was the only other positive spinal fluid finding which occurred with sufficient frequency to be of significance as a diagnostic aid. As shown in table 3, this was noted in 90 per cent of cases with jaundice; it was never found in patients without jaundice. The color varied in intensity from a faint yellow to a deep gold. This coloring is presumed to be due to bilirubin, which gains entrance to the spinal fluid in Weil's disease

as a result of the inflammatory changes in the meninges. In other diseases associated with icterus the spinal fluid does not become discolored unless the jaundice is severe and of long duration. We have recently observed two illustrative cases: one, a patient with Weil's disease, had xanthochromia at a time when his serum icterus index was only 27; the other, an infant with congenital atresia of the bile duct, had colorless spinal fluid at a time when the serum icterus index was 150. It appears, therefore, that xanthochromic spinal fluid in a patient with mild jaundice is a point in favor of the diagnosis of Weil's disease.

### THE DIAGNOSIS OF WEIL'S DISEASE

Any simple procedure which will assist in the early diagnosis of Weil's disease is of value. None of the usual diagnostic measures is entirely satisfactory. The demonstration of leptospirae in the blood is only possible during the first few days of illness, and in unskilled hands false positive reports are liable to occur. Guinea pig inoculation with blood or urine will only be positive if done at certain stages of the disease, and the procedure requires time and experience. The agglutination test is reliable, but a good antigen—preferably live leptospirae—must be available, and antibodies may not be demonstrable until late in the course of the infection. Biopsy of striated muscle reveals characteristic lesions in many instances,<sup>15</sup> and has, in our experience, been of considerable help in the diagnosis of Weil's disease.

### SUMMARY

Of 14 cases of Weil's disease observed during a four year period, 13 were found to have abnormal spinal fluid. In only six of these cases were there clinical signs which could be attributed to meningeal irritation.

A search of the literature revealed 78 comparable cases in which spinal fluid findings were given. In 65 of these abnormal spinal fluid had been found. Combined with the series of cases reported in this article the incidence of abnormal spinal fluid in 92 cases of Weil's disease was 78 (86 per cent).

The commonest abnormality was an increase in the cell count. Xanthochromia was noted in approximately 90 per cent of the cases in which jaundice was present.

Spinal fluid examination is of value as a routine diagnostic procedure when the diagnosis of Weil's disease is suspected.

### BIBLIOGRAPHY

1. ASHE, W. F., PRATT-THOMAS, H. R., and KUMPE, C. W.: Weil's disease. A complete review of American literature and an abstract of the world literature. Seven case reports, *Medicine*, 1941, xx, 145.
2. CLAPPER, M., and MYERS, G. B.: Clinical manifestations of Weil's disease, with particular reference to meningitis, *Arch. Int. Med.*, 1943, lxxii, 18.

3. WALCH-SORGDRAGER, B.: Leptospiroses, Bull. Health Organ. League of Nations, 1939, viii, 143.
4. COSTA, S., and TROISIER, J.: Virulence comparée du liquide cephalorachidien et du sang, Comp. rend. Soc. de biol., 1918, lxxxi, 1269.
5. MINKENHOF, J. E.: Meningisme bij leucaemie en bij ziekte van weil, Nederl. tijdschr. v. geneesk., 1937, iii, 4448 (Quoted by Walch-Sorgdrager).
6. COCHEZ, P., and FICHET: Nouvelles observations de spirochétose meningée anictérique, Presse med., 1933, xli, 646.
7. GOLDBERG, H. P., and DAVENS, E. D.: Weil's disease, Bull. Johns Hopkins Hosp., 1941, lxxviii, 112.
8. GARNIER, M., and REILLY, J.: Les réactions méningées au cours de la spirochétose ictérique, Compt. rend. Soc. de biol., 1917, lxxx, 446.
9. BRUNO, F. E., WILEN, C. J. W., and SNAVELY, J. R.: Spirochetal jaundice. A report of 15 cases, including 2 cases of *Leptospira canicola* infection, Jr. Am. Med. Assoc., 1943, cxxiii, 519.
10. BINGEL, A.: Zur Klinik und pathologischen Anatomie neurologischer Komplikationen bei Weilscher Krankheit, Deutsch. Ztschr. f. Nervenhe., 1936, cxli, 133.
11. BLOOM, N., and WALKER, H.: Spirochetal jaundice (Weil's disease), Virginia Med. Monthly, 1941, lxviii, 192.
12. CUSHING, E. H.: Leptospirosis icterohaemorrhagica, Jr. Am. Med. Assoc., 1927, lxxxix, 1041.
13. DAVIDSON, L. S. P., and SMITH, J.: Weil's disease (leptospirosis); clinical and bacteriological study of 19 cases occurring chiefly among fish workers, Brit. Med. Jr., 1934, ii, 1137.
14. STILES, W. W., GOLDSTEIN, J. D., and McCANN, W. S.: Leptospiral nephritis, Jr. Am. Med. Assoc., 1946, cxxxi, 1271.
15. SHELDON, W. H.: Lesions of muscle in spirochetal jaundice (Weil's disease; spirochetosis icterohemorrhagica), Arch. Int. Med., 1945, lxxv, 119.

# PRESSOR ACTIVITY OF DESOXYCORTICOSTERONE ACETATE IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS \*

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PREVIOUS studies <sup>1</sup> have demonstrated that the administration of desoxycorticosterone acetate (DCA) and sodium chloride to patients without hypertension or adrenal disease may be associated with an increase in blood pressure. Significant changes were not apparent until the second or third week of drug injection.

Because of the possibility that the adrenal cortex might be concerned in the development or maintenance of hypertensive vascular disease in man,<sup>2,3</sup> the blood pressure response of hypertensive individuals to DCA was compared to that observed in subjects without hypertension.

## METHODS

Observations were made on 10 normotensive subjects and 14 patients with uncomplicated hypertensive vascular disease on the wards of the Presbyterian Hospital and the Research Service, First Division, of the Goldwater Memorial Hospital. Age and sex distribution were similar in both groups. All patients were afebrile, free of albuminuria or renal complications. The hypertensive subjects had no history, signs, or symptoms of cardiac insufficiency, and the venous pressure was normal in all instances.

Blood pressures were measured each morning in the same arm by the same observer, with the subject in bed with a 30° elevation of the upper body. More than five readings (and usually seven or eight) were taken and the lowest systolic and diastolic values recorded. Preliminary observations were carried out for at least two weeks, followed by a final base line period of one week during which systolic and diastolic readings fluctuated within a range of 10 mm. of mercury or less.

All subjects were weighed before breakfast on the same scales. The daily fluid intake and urine output were recorded. Patients were given a constant diet and fluid intake, with the total dietary and added sodium chloride varying between 5 and 10 gm. a day but maintained constant for each subject by means of weighed salt shakers. DCA † was injected sub-

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cutaneously for one week in doses of 5 mg. twice daily. In five subjects of each group fasting blood samples for hematocrit, chloride, sodium and potassium determinations were obtained before and after one week of DCA administration and the serum volume measured with the blue dye T. 1824.

## RESULTS

The effect of DCA on normotensive and hypertensive subjects is shown in figure 1. The administration of this steroid for one week failed to alter the "resting" blood pressure significantly in the 10 members of the control group. In contrast, definite elevation of systolic and diastolic readings took place in one to four days in the 14 hypertensive individuals, the mean systolic rise reaching a maximum of 24 mm. of mercury on the sixth day, the mean diastolic rise 15 mm. of mercury.

The expected changes in weight and hemodilution which follow DCA administration were noted in both groups, together with slight reduction in urinary volume and evidence of chloride retention.<sup>4</sup> No consistent alteration in serum chloride or sodium values was observed, but reductions in serum potassium levels from 0.1 to 0.8 milliequivalents per liter were found in both series. The serum volume increased in the normotensive subjects and in four of the five hypertensive patients studied; the largest rise was in some of the controls in whom no significant blood pressure increase was noted. Electrocardiograms and teleroentgenograms taken before and after one week of DCA administration in three members of each group revealed no changes. In one of the hypertensive subjects in whom a marked rise in blood pressure followed DCA, ballistocardiographic tracings in the control period were unchanged after one week of drug injection.

## COMMENT

The rise in "resting" blood pressure observed within a few days after the sustained administration of DCA in hypertensive subjects cannot be ascribed alone to excessive retention of salt or water in the circulating blood. The weight, serum volume, hematocrit, urine volume and chloride changes were not more marked than those seen in normotensive individuals, in whom no significant pressor response was elicited during one week of DCA administration. The absence of alterations in the ballistocardiogram of one hypertensive patient points against a significant change in cardiac output in this subject.

Although the prolonged administration of DCA may give rise to a gradual increase in blood pressure in patients without hypertension or adrenal disease, it would appear that an accelerated response to DCA may be found in hypertensive vascular disease. Evidence is lacking as to whether the more immediate rise in blood pressure is a sequel to the hypertensive state, or is in some way related to its cause. Studies are in progress to determine the rôle of sodium chloride in this accelerated pressor response.

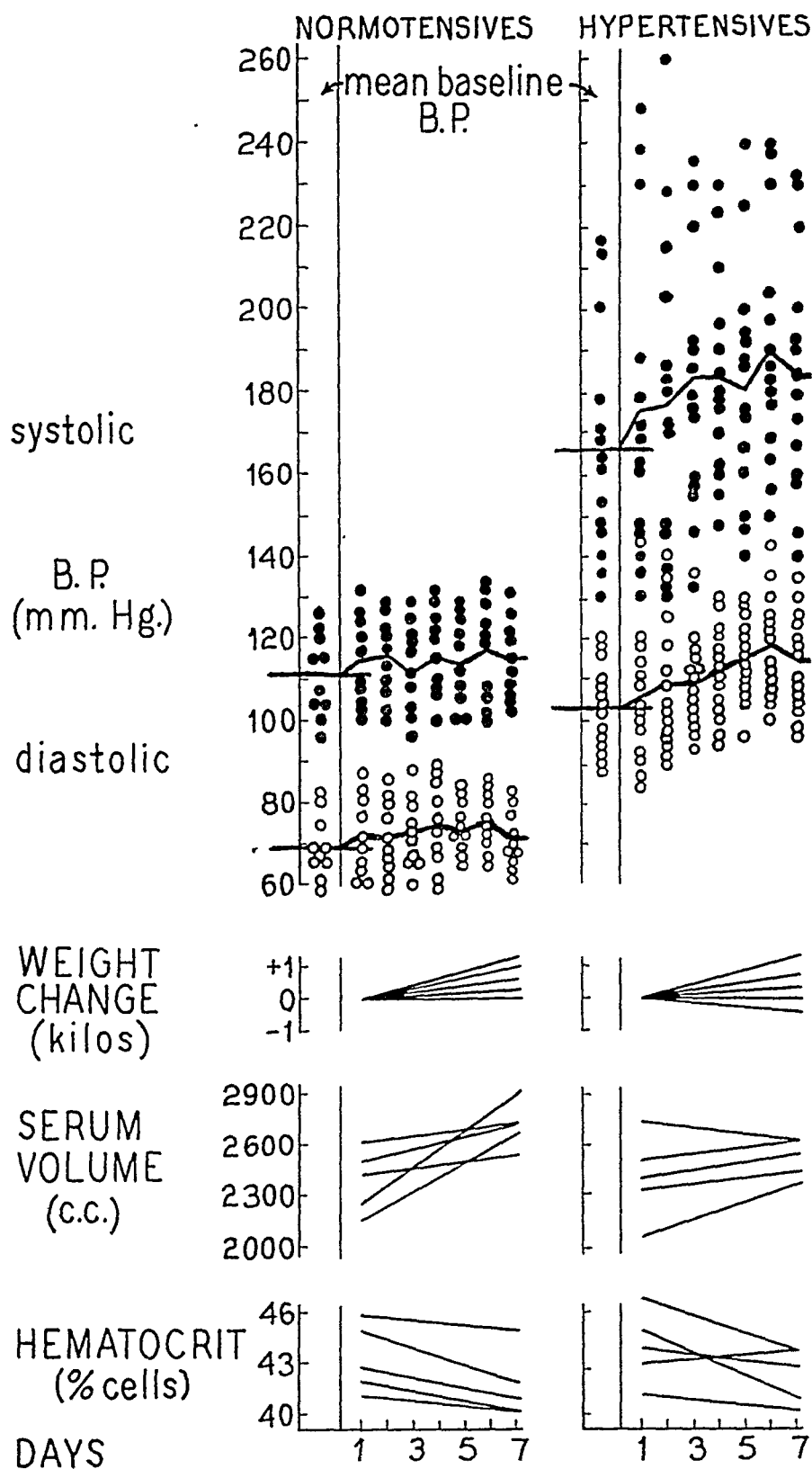


FIG. 1. Effect of DCA on normotensive and hypertensive subjects.

## CONCLUSIONS

1. Desoxycorticosterone acetate was administered to 10 normotensive subjects and 14 patients with uncomplicated hypertensive vascular disease in doses of 5 mg. subcutaneously twice daily for one week.

2. No significant change in "resting" blood pressure appeared in the normotensive group, whereas definite increases in systolic and diastolic readings were observed in the hypertensive patients.

3. The prompt rise in blood pressure of patients with hypertension could not be ascribed to changes in salt or water retention alone as there were comparable changes in the normotensive group.

## BIBLIOGRAPHY

1. PERERA, G. A., KNOWLTON, A. I., LOWELL, A., and LOEB, R. F.: Effect of desoxycorticosterone acetate on the blood pressure of man, *Jr. Am. Med. Assoc.*, 1944, cxxv, 1030-1035.
2. PERERA, G. A.: The relationship of the adrenal cortex to hypertension: observations on the effect of hypoadrenalism on a patient with hypertensive vascular disease, *Jr. Am. Med. Assoc.*, 1945, cxxix, 537-538.
3. PERERA, G. A., and BLOOD, D. W.: Disturbance in salt and water metabolism in hypertension, *Am. Jr. Med.*, 1946, i, 602-606.
4. CLINTON, M., JR., and THORN, G. W.: Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects, *Bull. Johns Hopkins Hosp.*, 1943, lxxii, 255-264.

**DISSECTING ANEURYSM OF THE AORTA:  
A REVIEW OF 17 AUTOPSIED CASES OF ACUTE DISSECTING  
ANEURYSM OF THE AORTA ENCOUNTERED AT THE  
MASSACHUSETTS GENERAL HOSPITAL FROM  
1937 TO 1946 INCLUSIVE, EIGHT OF WHICH  
WERE CORRECTLY DIAGNOSED  
ANTE MORTEM \***

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IN 1937 Glendy, Castleman, and White<sup>1</sup> presented a clinical and anatomical analysis of 19 cases of dissecting aneurysm of the aorta which had come to autopsy at the Massachusetts General Hospital over the period of 1897 to 1936, inclusive. In 13 of this number the dissection could be described as acute or directly related to the death of the patient, while in six it was discovered incidentally, the patient having died of other causes. In only two of the 13 acute cases had a correct antemortem diagnosis of dissecting aneurysm been established, and yet the authors felt that the clinical picture had been sufficiently dramatic in most instances to warrant consideration of such a process. Also, in order that this consideration, together with such diagnostic procedures as might be attempted on a seriously ill patient, should allow a correct clinical diagnosis to be made in a greater percentage, if not in the majority, of such cases, they particularly emphasized (1) the type of pain most likely to be encountered and its manner of onset and radiation (especially to the back), (2) the likelihood of collapse with a blood pressure maintained at hypertensive level, and (3) evidence of arterial obstruction due to involvement of aortic branches in the dissecting process.

In order to evaluate the results of the interest thus stimulated in the recognition of this condition clinically, we have made a comparative study in this hospital covering the subsequent 10 year period from 1937 to 1946, inclusive. For the sake of easy reference and comparison, we shall adhere in general to the plan of presentation adopted in the earlier article. No attempt shall be made to enter into a historical review of the subject nor to augment further the numerous attempts at detailed pathological classifications and descriptions of the underlying medial disease. For a comprehensive and dependable presentation of these topics, the reader is referred to Shennan,<sup>2</sup> Glendy, Castleman, and White,<sup>1</sup> Sailer,<sup>3</sup> and, for the most recent complete review, Leitch.<sup>4</sup> In the following discussion we shall adhere to the term "dissecting aneurysm of the aorta," as it is at present generally accepted in both its clinical and pathological aspects.

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The present report includes only those cases of dissecting aneurysm in which there had occurred a spontaneous rupture of the intima with either extensive medial dissection or unquestionable medial disease. During the 10 year period 1937 to 1946 seventeen such cases were encountered among 3,876 necropsies (0.44 per cent) at the Massachusetts General Hospital. All of these evidenced fresh dissection within the coats of the aorta, and in three there were found old, healed, dissected aneurysms as well. In seven of the 17 cases an antemortem diagnosis of dissecting aneurysm of the aorta had been established, and in an additional case (Case 5), who experienced two acute episodes of dissection, the diagnosis was correctly made during the first episode. In two of our cases in which the diagnosis was established only at necropsy there was a history of clinical syphilis with syphilitic heart disease, positive serology, and extensive antisiphilitic therapy. At necropsy these were the only two cases showing a limited aortic dissection based on medial disease and in addition presenting the typical findings of syphilitic aortitis.

TABLE I  
Seventeen Cases of Dissecting Aneurysm of the Aorta Coming to Autopsy  
at the Massachusetts General Hospital (1937 to 1946 inclusive)

Case No.	Sex	Age	Occupation	Necropsy No.	Year
1*	M	58	Clerk	8646	1937
2	F	78	?	8776	1938
3 <sup>5**</sup>	M	69	Executive	9189	1939
4 <sup>6</sup>	M	59	Chauffeur	9299	1939
5 <sup>7</sup>	M	49	Plumber	9360	1939
6	F	71	Housewife	9388	1939
7 <sup>8</sup>	M	58	Promoter	9791	1940
8 <sup>9</sup>	F	57	Housewife	9997	1941
9 <sup>10</sup>	M	49	Laborer	10023	1941
10 <sup>11</sup>	F	60	Housewife	10235	1941
11 <sup>12</sup>	M	52	Attorney	10322	1942
12 <sup>13</sup>	M	69	Physician	10460	1942
13 <sup>14</sup>	M	47	Merchant	10552	1942
14 <sup>15</sup>	M	49	Laborer	10964	1943
15 <sup>16</sup>	F	66	Housewife	11192	1944
16 <sup>17</sup>	M	59	Retired	11258	1944
17 <sup>18</sup>	M	50	Laborer	11850	1945

\* Negro.

\*\* The reference number indicates that this case has been previously published in "Case Records of the Massachusetts General Hospital."

Abstracted details of case histories and postmortem findings have been omitted for the sake of brevity. However, an individual chronological listing of the cases is presented (table 1), and the more important clinical and autopsy findings have been subsequently tabulated. Fourteen of these cases have already been published as individual case reports in "Case Records of the Massachusetts General Hospital" and are included in our references.<sup>5-18</sup>

## INCIDENCE, SEX, AGE, AND OCCUPATION

Glendy, Castleman, and White<sup>1</sup> reported the postmortem incidence of the acute type of dissecting aneurysm of the aorta, as one in 635 (table 2). In reviewing their figures on frequency of occurrence, it may be ascertained that for the fourth 10 year period, 1927-1936, the incidence was one in 376 for the acute type. In the present series of cases, all acute, there occurred one in 228 autopsies. No adequate explanation for this apparent increase in incidence has been forthcoming, and indeed it may be of little significance when compared with other reported series which also vary widely. Weiss<sup>10</sup> in 1935 reported a postmortem incidence of dissecting aneurysm of one in

TABLE II  
Postmortem Incidence of Dissecting Aneurysm of the Aorta  
at the Massachusetts General Hospital

Period	Necropsies	Cases Dissect. Aneurysm	Incidence
1937-1946	3876	17	1:228
1927-1936	3009	8	1:376
1897-1936	8255	13	1:635

300; McGeachy and Paullin<sup>20</sup> in 1937 of one in 500; Flaxman<sup>21</sup> in 1942 of one in 714; Sailer<sup>3</sup> in 1942 of one in 464; Logue<sup>22</sup> in 1943 of one in 143, and Leitch<sup>4</sup> in 1944 of one in 261. These figures could be misleading in that they may have been computed by different methods of analysis, and it may be said that the comparisons made in the table referred to here were based on comparable series in the same hospital.

The sex incidence in acute dissecting aneurysm is reported by various authors as ranging from two to one, to three to one, with the male sex predominating. This ratio is well maintained in the present series, in spite of the limited number of cases considered, there being 12 males and five females (table 3). It is interesting to note, however, that when the sex distribution

TABLE III  
Sex and Age Incidence

Sex	No. Cases	Age Extremes	Average Age
Male	12	47-69	55
Female	5	57-78	66
Total	17		59

is compared to that of age, females tend to dominate the upper age brackets. As shown, the age extremes among the males were 47 and 69 years, with an average of 55 years, while those of the females were 57 and 78, with an average of 66 years. This determines an overall age average of 59 years, which is in accord with other observations and is in nowise distorted by in-

clusion of the unusual cases encountered at extreme age levels. It is of further interest to realize that the sex-age relationship portrayed here resembles that found in other degenerative vascular conditions attended with vascular accidents.

Occupation and race appeared to be of little significance, with only four of this group falling in the laboring class and only one being a negro.

#### DATA AS TO PATIENT'S HISTORY AND FACTORS RELATED TO ONSET

A history of cardiovascular disease could be established in every case of this series. Arterial hypertension of either permanent or temporary character had been observed before the onset of aortic dissections in every instance. Congestive heart failure had occurred in four instances, angina pectoris was described in three others, and three of the patients had received antisyphilitic treatment. One of the latter, however (Case 1, negro, male), in whom systolic and diastolic aortic murmurs were present, had a consistently negative serological reaction and at autopsy showed no evidence of syphilitic infection. In the other two the presence of syphilitic disease was unequivocal. Such an incidence of syphilis complicated by dissecting aneurysm must be considered unusual.

A great deal of emphasis has been placed by some authors<sup>2, 23</sup> on the relationship of the acute onset of symptoms due to aortic dissection to physical exertion or emotional stress. An understanding of the process renders this a logical likelihood. However, in only two of the cases studied in the present analysis could the onset be clearly related to exertion; emotional disturbance seemed to play no part in any. In two there was a suggestive relationship between the onset and the eating of a meal.

#### SYMPTOMS AND SIGNS

The sudden onset of symptoms is generally considered characteristic of acute dissecting aneurysm of the aorta. Such an onset occurred in 14 of our 17 cases, and only in one could no history suggestive of the time of onset be obtained, while in two others gradually developing substernal pain was the initial warning. Pain was the initial symptom in 13 of the 16 cases of recognized onset, one was seized with sudden severe dyspnea, and in two syncope initiated the attack. In the remaining case, which presented congestive heart failure, it was not possible to find any symptom suggestive of the acute dissection found at necropsy.

At the onset or during the course of the acute episode, pain became the outstanding symptom in 15 of the 17 cases (table 4). In the majority of these it was persistent and often uncontrollable. Pain of dominating character was described as being substernal in four instances; in the back, usually in the interscapular region, in three; diffusely in the anterior part of the chest in six; and as being localized in the abdomen in two. Referred pain

was described in the back in five instances, in the arms in four, in the head and neck in three, in the legs in five, and in the abdomen once. It is to be recognized that the so-called referred pain was sometimes due to actual involvement of particular aortic branches in the dissecting process; especially did this seem to be true when the great vessels of the arch or the iliac arteries

TABLE IV  
Location, Occurrence, and Radiation of Pain

Location	Initial Occurrence	Radiation
Chest—substernal.....	4	
anterior (diffuse).....	6	2
back.....	3	5
Legs.....		5
Arms.....		4
Head and neck.....		3
Abdomen.....	2	1
No pain.....	2	
Total.....	17	

were involved. However, as will be considered later, pain of an altogether similar character often occurred when no such involvement of the corresponding vessels was demonstrable at autopsy.

Since pain is the leading symptom on which to base a clinical suspicion of the nature of the underlying process, a correlation of the manner of its onset and severity becomes as important in reaching a correct diagnosis as its location and spread. As may be seen (table 5), 10 of the 15 cases developed

TABLE V  
Manner of Onset and Severity of Pain

	No. of Cases
Manner of onset of pain:	
sudden (8 severe; shock in 4).....	10
gradual (none severe; shock in 1).....	5
no pain (shock in 1).....	2
Total.....	17
Severity of pain:	
severe (all sudden; shock in 4).....	8
moderate (2 sudden; shock in 1).....	7
no pain (shock in 1).....	2
Total.....	17

pain suddenly, and in eight of these pain was classed as severe. In every case in which the pain was classed as severe the onset was sudden. Four of the six cases who developed symptoms of severe shock fell into this sudden-severe pain group. In all five of the patients in whom pain developed gradually it was classed as moderate or subject to control, while of the seven who evidenced moderate pain only two had a sudden onset. Shock occurred in only one of those with gradual onset of pain in the moderately severe group. Rather unusual, it seems, for such a small series is the fact that two of the 17 patients complained of no pain at any time during the course of their ill-



ness. One of these (Case 11) evidenced shock and survived 48 hours after onset. The other (Case 6) was in congestive heart failure and possibly died at the moment of onset.

At some time during the course of the acute illness there developed other symptoms of prominence which could be considered compatible with, but not characteristic of, dissecting aneurysm. Severe shock occurred in six cases, in two of which the onset had been initiated by syncope. Dyspnea became an outstanding symptom in six cases but did not persist in the one who had evidenced it at onset. Aggravating nausea and vomiting occurred in three instances, and deep cyanosis developed in two.

### BLOOD PRESSURE

Considering a blood pressure above 140 mm. of mercury systolic and 90 mm. diastolic as abnormal, a history of hypertension was established in every case of this series. Case 10, which showed no cardiac enlargement clinically, by roentgen-ray or at necropsy had been observed in transient bouts of hypertension (table 6).

TABLE VI  
Blood Pressure Levels Before and After Onset of Final Episode

Blood Pressure	History	Observed Before	Observed After
Above 140 mm. systolic and 90 mm. diastolic	17	9	10
Below 140 mm. systolic and 90 mm. diastolic	0	0	4 (shock)
Not recorded	0	8	3
Total	17	17	17

Blood pressure readings were recorded in nine cases shortly before the onset of the final episode and in 14 after the onset. Of the latter number, the four individuals in whom the blood pressure was within normal limits or low, evidenced a state of shock. In the cases in whom the blood pressure was dependably recorded both before and after dissection there appeared to be a consistent drop in pressure, which, however, tended to remain at hypertensive levels. In one case only (Case 4) the blood pressure recorded after the accident was higher than before. It seems to us rather unusual that the diastolic pressure tended to fall out of proportion to the systolic pressure initially, with a consequent increase in pulse pressure, but the preëxisting wide pulse pressure mentioned as being a factor in producing intimal rupture could not be substantiated in this group. That the persistence of hypertensive levels in this condition may be considered as a differential point against coronary occlusion seems to be the general opinion, but no comparative studies of hypertensive patients incurring coronary accidents have been found. However, Chambers<sup>24</sup> in studying 100 cases of acute myocardial infarction, con-

firmed by positive electrocardiographic findings, states that hypertensive patients suffering this accident showed a consistent drop in blood pressure, which, however, tended to remain at hypertensive levels. It would seem, therefore, that the initial level of blood pressure might determine in the absence of shock the levels observed after onset in both these conditions and that the apparent discrepancy is based on the fact that the incidence of hypertension is much greater in dissecting aneurysm and the survival period far shorter.

### HEART SIZE

To facilitate comparison of heart size as determined clinically, by roentgen-ray, and at autopsy, these observations have been tabulated in table 7.

TABLE VII  
Observations on Heart Size

Method	Normal Size	Enlarged	No. of Cases
Clinical	2	13	15
Radiographic	3	5	8
Anatomic (weight)	1	16	17

In the 15 cases on which such observations were recorded, the heart was reported as being enlarged on physical examination in 13 and normal in two. Of the eight cases examined radiologically, five were reported as showing cardiac enlargement and three normal heart size. At autopsy 16 of the 17 cases studied showed a definite increase in heart weight well above normal, associated with left ventricular hypertrophy. In the one instance (Case 10) which did not show any cardiac abnormality, the heart had been recorded as of normal size both clinically and by roentgen-ray. It will be remembered that this patient gave a history of only transitory hypertension.

### HEART MURMURS

Auscultatory findings were described in 16 of the cases presented. Murmurs were heard over the basal area in nine of these patients, a diastolic murmur alone in two, and both systolic and diastolic in seven (table 8). In one of the last-mentioned, systolic and diastolic murmurs were heard also at the apex. In four cases (1, 6, 9, 14), including the two with syphilis, the diastolic murmur at the base had been heard prior to the onset of aortic dissection. In five cases (5, 7, 8, 13, 17) it was recorded as having been heard after the onset, but in only two of these (Cases 5 and 17) was it definitely determined to have been absent previously.

An attempt to correlate the incidence of aortic diastolic murmurs with the accident of dissection on such data would be misleading; yet one cannot escape the fact that the ratio is much higher than might be expected among average hypertensive patients.

Evidence of minimal disease of the aortic leaflets was determined at autopsy in eight instances, six of which were of a sclerotic and two of an inflammatory nature. There was no correlation to be drawn between these changes in the aortic leaflets and the existence of the basal diastolic murmurs, as in six of the cases presenting murmurs the leaflets were described as being normal.

TABLE VIII  
Incidence and Types of Cardiac Murmurs in 16 Cases

Murmur	Apical	Basal	No. of Cases
Systolic alone	3	0	3
Diastolic alone	0	2	2
Systolic and diastolic	1	7	8
None			3

In view of the foregoing, we believe that the presence of a diastolic murmur at the base may take on an added significance when the clinical picture warrants suspicion of aortic dissection.

#### OTHER PHYSICAL FINDINGS

Other physical findings to which may be attributed particular significance in this condition are those associated with the involvement of the aortic branches in the dissecting process. This is especially true in involvement of the carotid arteries giving rise to cerebral manifestations and of the iliacs suggesting embolism. When the latter occurs initially, it is not unusual for operative relief to be attempted, as happened in one of these cases (Case 8). Such signs when added to a clinical picture otherwise suggesting aortic dissection may easily become pathognomonic. However, their occurrence is not sufficiently common (five in 17 cases) to warrant awaiting their development to venture a positive diagnosis.

#### TEMPERATURE, PULSE, AND RESPIRATION

In this series of cases there occurred no extreme variations in temperature, pulse, or respiration. In the absence of shock, a moderate increase above normal in all three was the usual finding. The maximum temperature recorded was 102° F., and the highest pulse rate 120. The heart rhythm was uniformly regular.

#### LABORATORY FINDINGS

The white cell count recorded in five of our cases ranged from 10,000 to 15,500, with a moderate increase in polymorphonuclear cells. Blood counts had not been done sufficiently frequently to indicate any significant drop in red cells, even though such might have occurred. The Hinton serological

reaction was determined in five cases and found to be positive in two of the three which had previously been diagnosed as having syphilitic infection. In five of the six patients on whom urine analyses were done there occurred abnormal amounts, alone or in combination, of albumin, and of red blood cells, white blood cells, and casts in the sediment. There seemed to be no consistent correlation between these findings and the involvement of the renal arteries by the dissecting process, but red blood cells in the urine following a period of anuria in one of the cases was probably due to involvement of a renal artery.

The electrocardiogram was recorded at least once in 14 of the 17 cases. There was slight to marked left axis deviation in 12 of these and a definite pattern of "left ventricular strain" in seven. There were additional changes in four which suggested the presence of coronary heart disease. The tracings in no case could be considered entirely normal and yet changes definitely suggestive of an acute myocardial infarction were never present. This was consistently true even in those cases in which the coronary arteries themselves were involved in the dissection.

The incidence of cardiac enlargement by roentgen-ray study has already been considered. Tortuosity of the aorta was described in seven of the eight cases examined, and in four of these dilatation was also present. In three instances in which successive roentgenological examinations were made changes in size or contour of the aorta were discovered, and in one of these it was reported as being compatible with dissection of the aorta.

### CLINICAL DIAGNOSIS

Seven of the 17 cases came to autopsy with a diagnosis of dissecting aneurysm of the aorta (table 9). The diagnosis was made at one time in another case which merits a special note. This patient (Case 5) survived

TABLE IX  
Clinical Diagnosis

Dissecting aneurysm.....	8*
Acute coronary occlusion.....	4*
Rupture of a non-dissecting thoracic aneurysm.....	3
Malignant hypertension with hypertensive encephalopathy.....	1
Embolism.....	1
Congestive heart failure.....	1
Total.....	18*

\* One case with two separate episodes of aortic dissection was correctly diagnosed once and mistaken for acute coronary occlusion the second time.

17 months after his first dissection, which was rightly diagnosed, but the second dissection, which occurred five and a half days before death, was thought to be an acute coronary occlusion. (This case appears under both diagnoses in table 9.) A final diagnosis of coronary occlusion, which condition is most frequently confused with dissecting aneurysm, was made in

four instances. Three cases were diagnosed as having rupture of a thoracic aneurysm, two of which were thought to be due to syphilitic involvement and the third to an arteriosclerotic process. Malignant hypertension with hypertensive encephalopathy was considered as the primary cause of death in one, embolism in the leg in another, and congestive heart failure in the remaining case.

### SURVIVAL

The estimated period of survival is based on the length of life following the onset of the terminal episode. A special reference is added for the three cases which survived by three months, 17 months, and four and one-half years their initial dissection (table 10). Nine died within the first 24 hours

TABLE X  
Period of Survival After Onset

Survival Period	Acute Dissecting Aneurysm	Old Dissecting Aneurysm
24 hours and less.....	9	
1 day to 6 days.....	6	
3 months.....	?	1
17 months.....	(5.5 days)	1
4.5 years.....	(sudden death)	1
unknown.....	2	
Total cases.....	17	
Average.....	43 hours	

and six within one to six days, with an average survival of 43 hours after the onset of the terminal episode. In their paper Glendy, Castleman, and White<sup>1</sup> reported a survival period for the acute cases of 4.15 days. This survival period is twice as long as ours, and we are unable to explain the discrepancy. The actual survival time in two instances could not be established (Cases 6 and 14). Of the three with healed dissecting aneurysms, one survived the initial episode by 17 months (Case 5) and another by 4.5 years (Case 16). The last case mentioned presented a second healed dissected aneurysm which had no doubt occurred three months before his last accident. In the third case, which survived the first episode by three months, the survival time of his terminal attack could not be determined.

### ANATOMICAL CAUSE OF DEATH

The underlying cause of death was considered by the pathologist to be acute dissection of the aorta in every case, but in only two of the 17 could it be considered the immediate cause of death. In the other 15 death was no doubt primarily due to hemorrhage into serous or tissue spaces, with or without demonstrable rupture of the adventitia (table 11). The most frequent, as usually described, was hemorrhage into the pericardial sac with cardiac tamponade which occurred in 14 of our 17 cases. In three of this number the hemorrhage into the pericardium was associated with hemorrhage into

the left pleural space, in two into the mediastinum, and in two into the peritoneal cavity. In only one instance was there hemorrhage into other areas, namely, mediastinum and left pleural space, in which the pericardial sac was not involved. Thus, in this series, it can be stated that rupture into the pericardium with resulting cardiac tamponade was by far the most frequent im-

TABLE XI  
Location of External Hemorrhages

Pericardium.....	14
Pleural spaces.....	4
Mediastinum.....	2
Peritoneum.....	2

mediate cause of death, which is in accord with the stated conclusion of many others. The remaining two cases, as noted above, died without external hemorrhage from the aortic wall.

#### LOCATION OF INITIAL AND SECONDARY TEARS

Tears in the aortic intima, classified as initial, were located in the upper aorta in 19 instances, 16 of which presented evidence of recent occurrence, the other three having appeared to be well healed and communicating with dissected endothelialized aneurysmal sacs (table 11). Eleven of the 19 initial intimal tears were located within the first three centimeters of the ascending aorta, six in the ascending aorta beyond the 3 cm. level, one in the arch, and the remaining one in the thoracic aorta.

TABLE XII  
Location of Initial and Secondary Tears in the Aortic Wall

Location	Intimal	Adventitial	Rerupture into Arterial Lumen
In first 3 cm. of ascending aorta	11 (2 old)	13	
In ascending aorta beyond 3 cm.	6	0	
In aortic arch	1	0	
In descending thoracic aorta	1 (old)	2	
In abdominal aorta			2
In iliac arteries			4
Total	19	15	6

It was more difficult to identify the site of the rupture of the adventitia through which blood escaped from the sac into the surrounding tissues or serous cavities. Sometimes it seemed that there had occurred a separation of the fibers of the outer coat, permitting diffuse penetration of blood, rather than a definite rupture of the coat. Of the 15 instances in which rupture of the adventitia with hemorrhage could be localized, 13 had occurred within the first 3 cm. of the ascending aorta, and the majority of these at the approximate level of the accompanying intimal tear. In two instances the

rupture had occurred in the thoracic portion of the aorta. In two instances the hemorrhage had extended along the adventitia of the pulmonary arteries, even reaching the lung parenchyma.

Rerupture of the dissecting aneurysmal sac into the original lumen was discovered in six instances, in two of which the secondary tear had occurred in the abdominal portion of the aorta and in the other four in one of the iliac arteries. Two of the cases (Cases 5 and 16) showing rerupture into an arterial lumen, both by way of the iliac arteries, had survived the initial episode by 17 months and four and a half years respectively. The other healed dissecting aneurysm (Case 14) apparently had been quite limited during the initial episode, the exact time of which is thought to have been three months before the final illness. It was believed that the terminal episode in this case was due to a marked extension through the original tear without rerupture into the aorta having ever occurred. The other four cases (4, 11, 12, 13) showing rerupture into an arterial lumen during their terminal episode survived the onset by 12, 24, 48, and 96 hours respectively. The idea that rerupture of dissecting aneurysm into an arterial lumen increases the chances of survival is no doubt based on the fact that most cases in which complete healing occurs show a free secondary communication between the sac and the lumen. That so many patients succumb in the initial attack in spite of such a communication would indicate that its occurrence is not the overall determining factor in length of survival after onset.

#### EXTENT OF AORTIC DISSECTION AND INVOLVEMENT OF OTHER BLOOD VESSELS

For the purpose of classification only the length of the aortic dissection is considered. It is recognized that the extent of dissection around the aorta is just as important from the standpoint of correlation with aortic branch involvement, but its variability renders description difficult except where it is

TABLE XIII  
Extent of Aortic Dissection and Involvement of Other Blood Vessels

Length of Dissection	No. Cases	Coronary	Vessels of Arch	Celiac Axis	Renal	Mesenteric	Iliac
Limited	2	1					
Moderate	3		1				
Extensive	12	2	5	5	6	5	8
Total	17	3	6	5	6	5	8
Incidence of related symptoms		2	6	1	1?	2	6

complete or almost so. Thus we have considered the extent of dissection as limited when it involved only the ascending aorta, as moderate when it included the arch as well, and as extensive when it involved the aorta beyond the arch (table 13). In only the two cases (9 and 14) in which syphilitic

aortitis was present had the dissecting process been limited to the ascending aorta. That localized fibrosis of the media due to the syphilitic process tends to limit dissection along this otherwise diseased coat has been mentioned several times.<sup>1, 2, 25</sup> Dissection described as moderate had occurred in three instances, and in the other 12 the dissection had extended to or beyond the bifurcation of the abdominal aorta.

Considering involvement of the main branches of the aorta in the dissecting process in order of frequency, the iliac arteries were affected in eight cases, the great vessels of the arch in six, the renal arteries in six, the celiac axis in five, the mesenteric arteries in five, and the coronary arteries in three. That symptoms suggesting extension of the dissecting process into these arteries are not always evident has already been mentioned. A correlation between instances of actual vessel involvement and symptoms presumably consequent thereto is shown in table 13. Symptoms suggesting the possibility of such vessel involvement with no comparable lesion demonstrable at autopsy occurred in the legs in one case, head and neck in two, and abdomen in two.

An arteriosclerotic involvement of some part of the aorta was described in every case. Medionecrosis, which is now recognized as being by far the main etiologic factor of dissection of the aorta, was found in 13 cases; it was not typical in two cases and was absent in the other two cases.

## DISCUSSION

The increasing frequency with which a correct antemortem diagnosis is being made in dissecting aneurysm of the aorta within the past decade seems to be well brought out in this report. There is no doubt that this is primarily due to the widespread interest created in this condition by the work of Shennan.<sup>2</sup> He was able to report only a 2 per cent correct antemortem diagnosis in his review of 300 cases (1934). This interest was given an added impetus in this hospital through the efforts of Glendy, Castleman, and White,<sup>1</sup> who reported a correct antemortem diagnosis in 15 per cent of their small series (1937). Leitch<sup>4</sup> collected 282 cases, which included all those having occurred after Shennan's report to the time of his publication (1945). In 56, or 20 per cent, of these cases a correct antemortem diagnosis had been made. In the present series the condition had been clinically established in 41 per cent and suspected in another case in whom, during a previous accident, the diagnosis was rightly made.

The extension of pain from its initial location, which is usually in the thorax, to the head and neck, back, abdomen, or lower limbs, while often of an almost pathognomonic value, should not be considered necessary to make the diagnosis of dissecting aneurysm. In the light of our findings it would appear that associated pain in the arms should not be given too much emphasis in differentiating dissecting aneurysm from acute coronary occlusion without other evidence, particularly electrocardiographic.



## CONCLUSIONS

1. A clinical and anatomical analysis of 17 cases of acute dissecting aneurysm of the aorta occurring at the Massachusetts General Hospital over the past 10 years (1937 to 1946) is presented.

2. A correct antemortem diagnosis was made in eight instances, in one of which a second and fatal attack was wrongly interpreted.

3. The manner of onset and the severity and spread of pain are the most reliable symptoms on which to base a diagnosis of dissecting aneurysm.

4. A history of hypertension has been established in every individual of this series. Evidence of hypertensive heart disease was found in all but three cases, two of which showed syphilitic heart disease.

5. Basal heart murmurs, particularly diastolic, were encountered sufficiently often to warrant consideration of their diagnostic significance.

6. The absence of characteristic electrocardiographic changes suggesting myocardial infarction should be given much weight in reaching the diagnosis of dissecting aneurysm in equivocal situations.

7. In spite of the fact that a definite diagnosis is not always easily reached, even when the condition is suspected, there has been a marked increase in the antemortem recognition of dissecting aneurysm during the past decade.

We wish to express our appreciation to Dr. Benjamin Castleman for his painstaking analyses of this condition in the cases presented and for his helpful criticism of the manuscript.

## BIBLIOGRAPHY

1. GLENDY, R. E., CASTLEMAN, B., and WHITE, P. D.: Dissecting aneurysm of the aorta, *Am. Heart Jr.*, 1937, xiii, 129.
2. SHENNAN, T.: Dissecting aneurysms, 1934, H. M. Stationery Office, London.
3. SAILER, S.: Dissecting aneurysm of the aorta, *Arch. Path.*, 1942, xxxiii, 704.
4. LEITCH, W. H.: Dissecting aneurysm, *Bull. School Med., Univ. Maryland*, 1944, xxix, 7.
5. Clinico-pathological Cases: *New England Jr. Med.*, Case 25382, 1939, ccxxi, 471.
6. *Ibid.*, Case 26341, 1940, ccxxiii, 294.
7. *Ibid.*, Case 28072, 1942, ccxxvi, 273.
8. *Ibid.*, Case 27022, 1941, ccxxiv, 77.
9. *Ibid.*, Case 27292, 1941, ccxxv, 116.
10. *Ibid.*, Case 27302, 1941, ccxxv, 155.
11. *Ibid.*, Case 28111, 1942, ccxxvi, 456.
12. *Ibid.*, Case 28202, 1942, ccxxvi, 828.
13. *Ibid.*, Case 28421, 1942, ccxxvii, 603.
14. *Ibid.*, Case 28442, 1942, ccxxvii, 680.
15. *Ibid.*, Case 29451, 1943, ccxxix, 757.
16. *Ibid.*, Case 30212, 1944, ccxxx, 651.
17. *Ibid.*, Case 30341, 1944, ccxxx, 300.
18. *Ibid.*, Case 32062, 1946, ccxxxiv, 196.
19. WEISS, S.: Clinical course of spontaneous dissecting aneurysm, *Med. Clin. N. Am.*, 1935, xviii, 1117.

20. McGEACHY, T. E., and PAULLIN, J. E.: Dissecting aneurysm of the aorta, *Jr. Am. Med. Assoc.*, 1937, cviii, 1690.
21. FLAXMAN, N.: Dissecting aneurysm, *Am. Heart Jr.*, 1942, xxiv, 654.
22. LOGUE, R. B.: Dissecting aneurysm, *Am. Jr. Med. Sci.*, 1943, ccvi, 54.
23. CECIL, R. L.: Textbook of medicine, 6th ed., 1943, W. B. Saunders Co., p. 1164.
24. CHAMBERS, W. N.: Acute myocardial infarction (a study of 100 consecutive cases), *New Eng. Jr. Med.*, 1946, ccxxxv, 347.
25. RITVO, M., and VOTTA, P.: Dissecting aneurysm, *Am. Jr. Roentgen.*, 1944, lii, 583.
26. GRAYBIEL, A., and SPRAGUE, H. B.: Dissecting aneurysm of the aorta; case report of negro with aortic regurgitation and saccular aneurysm of aorta of nonspecific origin, *Am. Heart Jr.*, 1941, xxi, 530-533.

# THE USE OF FOLIC ACID IN THE TREATMENT OF ANEMIA OF RHEUMATOID ARTHRITIS— A PRELIMINARY REPORT \*

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## INTRODUCTION

It is well established on sound evidence that rheumatoid arthritis is a systemic disease.<sup>1, 2, 3, 4</sup> The most dramatic manifestation is usually a polyarthritis. However, associated fever, anorexia, weight loss, muscle atrophy, iritis, elevated sedimentation rate, and anemia, and the often dramatic relief with jaundice,<sup>5, 6</sup> or pregnancy,<sup>7</sup> prove conclusively its generalized nature.

Of all the associated symptoms of rheumatoid arthritis almost consistently present is a hypochromic microcytic anemia of an appreciable degree.<sup>8, 9, 10</sup> Of 50 cases of rheumatoid arthritis chosen at random from our files the average initial hemoglobin before treatment was 11.04 grams, the average erythrocyte count was 4,550,000, and the color indices averaged 0.82. Of these 50 patients those with the more severe form of the disease had a corresponding anemia of a more profound degree with hemoglobins of below 9.0 grams, erythrocyte counts of normal range and color indices, therefore, averaging below 0.70. This same blood picture has been observed by others.<sup>8</sup> Because of this almost universal presence of a significant anemia the rôle of hematinics assumes one of importance in the treatment of rheumatoid arthritis. We certainly agree with Hench et al.<sup>11</sup> that there is no rationale to the policy of treating the anemia and allowing the arthritis to take care of itself. Multiple therapeutic agents must be utilized with the emphasis altered to suit the individual patient,<sup>12, 13, 14, 15</sup> but there is hardly a patient with rheumatoid arthritis who escapes a prescription for an hematopoietic agent. Iron is reported effective, usually in large but poorly tolerated dosages,<sup>16, 17, 18</sup> but in the usual amounts iron exerts no benefit.<sup>8, 19, 20, 21</sup> Antianemic therapy with liver injections, either with the crude or purified preparations, in our experience fails appreciably to influence the blood picture. Transfusions, though time consuming, expensive, and occasionally hazardous, provide the only certain method of even temporarily improving this resistant anemia.<sup>13, 17, 15, 19, 22</sup>

Folic acid has recently been shown by Spies et al. to be highly effective in the treatment of Addisonian pernicious anemia in relapse<sup>23, 24, 25, 26</sup> and in

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the treatment of sprue.<sup>26, 27, 28, 29</sup> It is also efficacious in treating the macrocytic anemias of pregnancy<sup>26</sup> and of nutritional deficiencies.<sup>23, 30</sup> It is reported effective in some cases of aplastic anemia following roentgen therapy<sup>31</sup> but apparently has no effect on the hypochromic microcytic anemias due to iron deficiency, myelophthisic or idiopathic states.<sup>24</sup>

Nevertheless, because the anemia of rheumatoid arthritis is, like the disease itself, of unknown etiology, and because it is so resistant to the usual hematopoietic agents, it was thought to be worthwhile to investigate the effect of folic acid as an antianemic factor in patients suffering with rheumatoid arthritis.

### METHOD OF STUDY

Twenty patients with indisputable rheumatoid arthritis were selected for study. Both male and female patients were included in the group and the ages varied from 14 years to 70 years. The average duration of the disease before starting the study was 10.52 years. Nineteen patients had previously received iron and/or liver in the usual therapeutic doses without appreciable benefit; transfusions in some instances had been given at intervals with unsustained correction of the anemia. The patients were divided into two groups consisting of 10 patients each. Group I received five milligrams of folic acid by mouth four times daily and all other hematinics were stopped. Group II received orally five milligrams of folic acid four times daily plus oral ferrous salts in dosages of 200 milligrams of metallic iron per 24 hours.

Initially the peripheral blood was examined in all patients and the determinations of hemoglobin by two methods,<sup>32, 33</sup> a total erythrocyte count, total and differential leukocyte counts, reticulocyte count,<sup>34</sup> sedimentation rate,<sup>35, 36</sup> and hematocrit<sup>33</sup> were determined. These studies were repeated on the fourteenth, thirtieth, sixtieth, and ninetieth days of treatment. Reticulocytes were counted on the second, third, fourth, sixth, eighth, fourteenth, thirtieth, sixtieth, and ninetieth days. Each patient was questioned for the development of toxic manifestations and for the effect of folic acid on the underlying disease symptomatology.

Those patients who failed to exhibit any response were reexamined for blood loss or excessive blood destruction and gastric analyses were performed for the determination of the presence of free hydrochloric acid. Additional folic acid was then given to these "failures."

### RESULTS

The 10 patients with rheumatoid arthritis who received five milligrams of folic acid four times daily for 90 days (Group I) exhibited during the first two weeks an appreciable reticulocytosis, the appearance of a significant number of immature leukocytes and erythrocytes, a rise in the mean corpuscular volume, the color index, and the hematocrit (figure 1). There was a consistent rise in the monocytes. The erythrocytes showed only slight

increase (figure 1). The mean average rise in the hemoglobin in two weeks' time was 0.496 gram with a range of minus 0.14 to plus 1.65 grams; of the 10 patients five (50 per cent) had a definite increase in hemoglobin and an equal number showed no significant response. During the same period the reticulocytes rose from an initial mean average of 1.83 per cent to a mean average of 4.22 per cent with the maximum reticulocytosis appearing on the eighth day of treatment. The mean average hematocrit

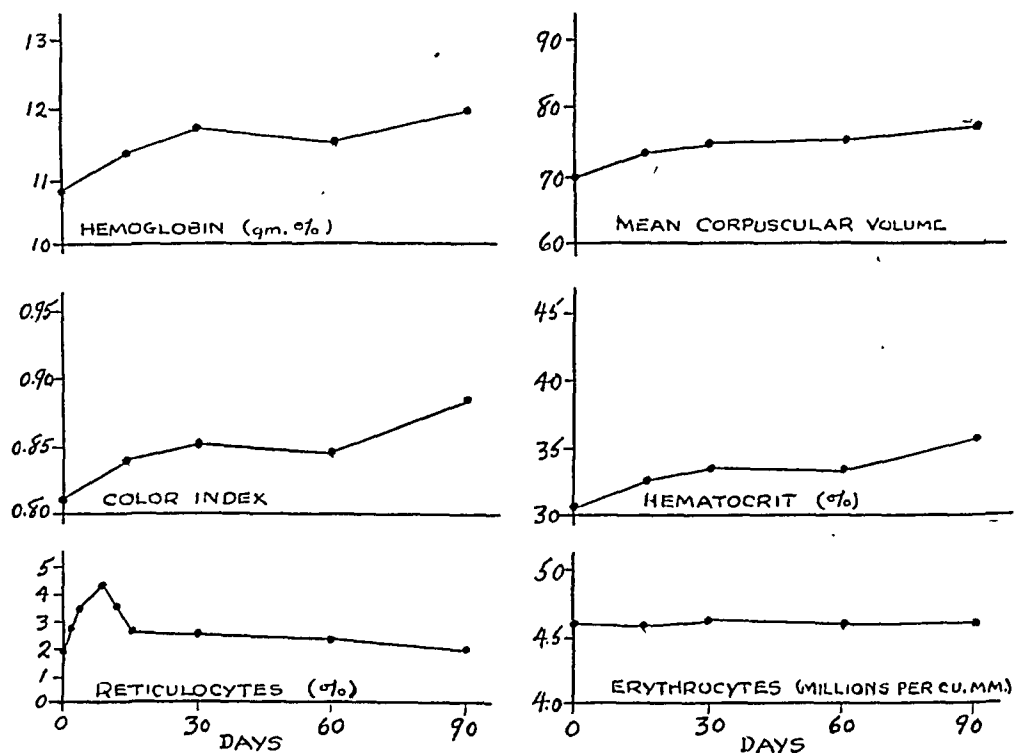


FIG. 1. Mean average blood values of 10 patients—Group I.

rise in two weeks' time was 1.87 per cent and the mean average color index increased 0.029. The erythrocytes rose only 22,000 in an average of 10 patients and the mean corpuscular volume at the end of two weeks was increased from 69.1 to 72.5. The total leukocyte count was not significantly altered and the differential count exhibited no change except for (1) the appearance of immature forms (table 1), and (2) the increase in monocytes from 3.2 per cent to 4.5 per cent.

The over all general improvement in the blood picture noted at the end of two weeks of treatment showed even further gain at the end of one month. The hemoglobin increased during the second two weeks a mean average of 0.375 gram, the hematocrit rose an additional 1.05 per cent, the erythrocytes increased only a mean average of 89,000 but the color index rose an additional 0.015; the reticulocytes exhibited a persistent increase with a mean average level of 2.68 per cent and the mean corpuscular volume again rose

reaching a level of 73.9. The monocytosis persisted at a level of 5.8 per cent. Of special note was the confirmation of the finding of immature forms which in four weeks averaged 1.5 per cent (table 1). At the end of 30 days seven patients (70 per cent) demonstrated a significant rise in hemoglobin and in other blood determinations as noted. Three patients (30 per cent) showed no improvement.

TABLE I  
Immature Cells (Groups I and II)

Erythrocyte Series	Initial	14-day	30-day	60-day	90-day
Metakaryocyte (Normoblast)	0	0	1	1	0
Karyocyte (Pronormoblast)	0	4	3	1	2
Prokaryocyte (Erythroblast)	0	5	3	1	0
Karyoblast (Megaloblast)	0	0	0	0	0
Granulocyte Series					
Metagranulocyte (Metamyelocyte)	0	2	5	0	0
Granulocyte (Myelocyte)	0	5	5	4	3
Progranulocyte A (Promyelocyte II)	0	2	6	1	3
Progranulocyte S (Promyelocyte I)	0	0	2	0	0
Granuloblast (Myeloblast)	0	0	0	0	0
Lymphocyte Series					
Prolymphocyte	0	8	4	8	4
Lymphoblast	0	0	0	0	0
Monocyte Series					
Promonocyte	0	0	2	0	0
Monoblast	0	0	0	0	0
Total	0	26	31	16	12

In 60 days the peripheral blood determinations exhibited further alterations. The hemoglobin fell slightly to a mean average value of 11.32 grams. The total erythrocyte count was essentially the same; hence the color index fell to a mean average of 0.852. The hematocrit exhibited a slight rise and the mean corpuscular volume rose to a mean average of 74.5. The reticulocytes were maintained at a level of 2.6 per cent; the monocytes remained at a level of 5.6 per cent and the immature forms were still present in eight cases.

At this point the group was subdivided into those patients who had responded and those who had exhibited no change or were worse. Three patients of the 10 fell in to the latter category and the dose of folic acid was increased in these from 20 milligrams daily to 100 milligrams daily. Those who had shown a response were maintained on the 20 milligram daily dose.

The three patients of this group whose blood values had shown no improvement on the smaller dosage exhibited a startling improvement on the

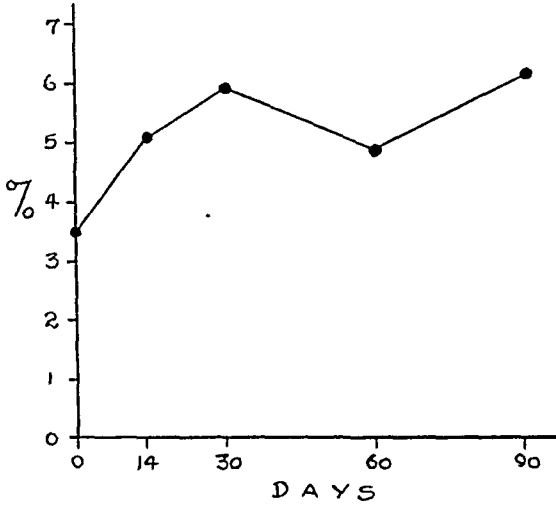


FIG. 2. Monocyte levels—Groups I and II.

larger dose (figure 3). The hemoglobin rose to 12.01 grams, and the erythrocytes remained roughly the same; therefore, the color index rose to 0.85. The hematocrit increased to 34.43 per cent and the mean corpuscular volume went up to 71. The reticulocytes remained at 2.2 per cent and the monocytes rose to 7.1 per cent. On examination of the stained smears the erythrocytes

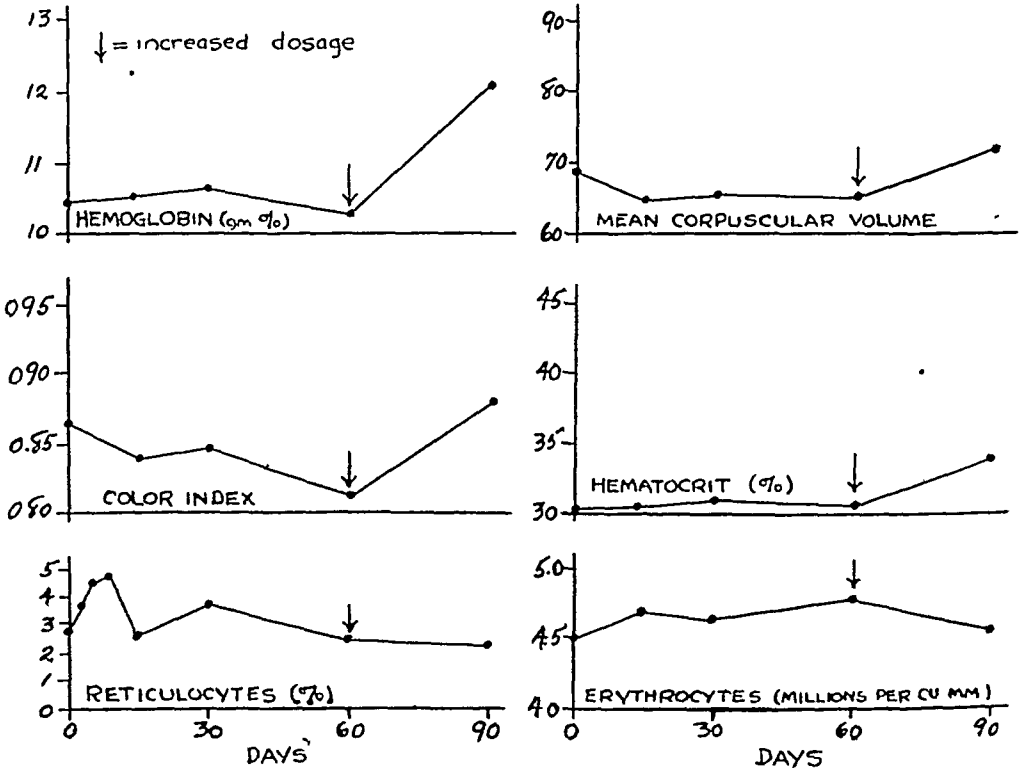


FIG. 3. Mean average blood values of 3 "failures"—Group I.

were rounder, showed less variation in size and shape and the stain was fixed with more uniformity and intensity.

In all 10 patients at 90 days the hemoglobin had risen to a mean average of 11.89 grams, the erythrocytes remained relatively constant, and the color index increased by 0.036 to 0.888. The reticulocytes were still above the initial mean average value at 2.26 per cent and the immature forms were still present in an increased percentage of 0.77 per cent. The hematocrit rose 1.24 per cent to a value of 35.50 per cent and the mean corpuscular volume rose 2.0 to a level of 76.5. Morphologically the red cells were more normal in appearance.

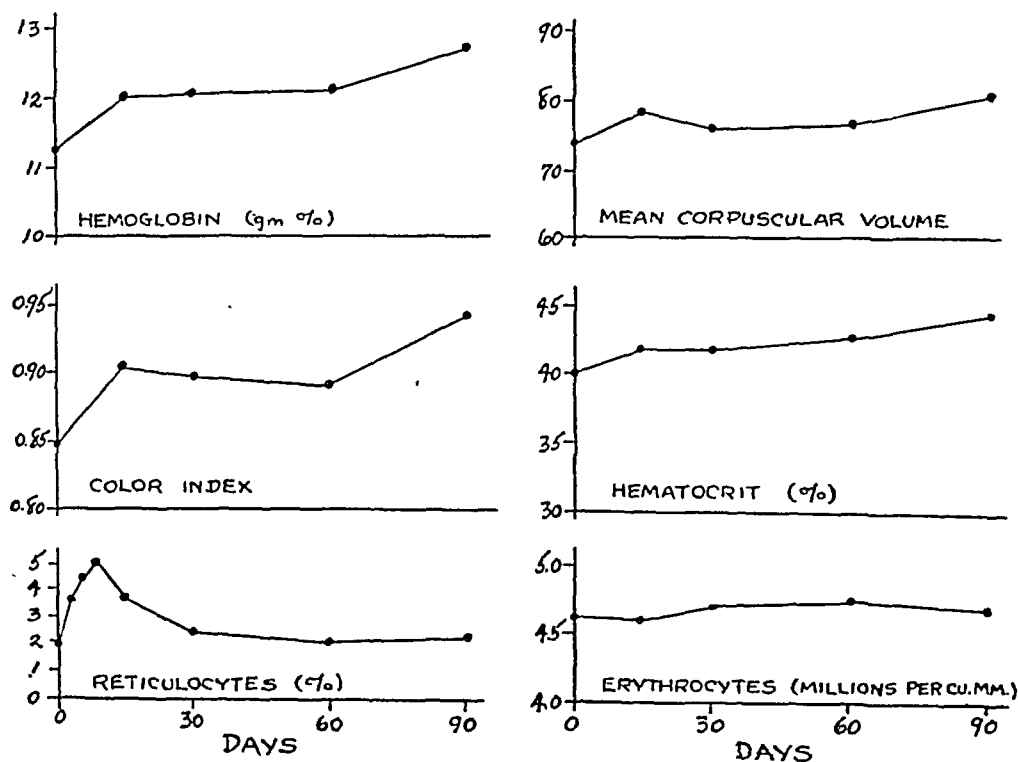


FIG. 4. Mean average blood values of 10 patients—Group II.

The blood picture in 10 patients with rheumatoid arthritis given both folic acid, five milligrams four times daily, and iron salts equivalent to two hundred milligrams of metallic iron daily (Group II) varied from that seen in Group I in that during the first two weeks there was a greater response (figure 4). The hemoglobin rose 0.881 gram, the hematocrit rose 1.92 per cent, on the eighth day the reticulocytes were at a level of 5 per cent and were still elevated on the fourteenth day at 3.54 per cent, the color index gained 0.063 and the mean corpuscular volume rose from 74 to 78. The total erythrocytes decreased a mean average of 9000. The monocytes increased to 5.7 per cent. Of the 10 patients in Group II 80 per cent showed a significant improvement in the blood picture.



Continuation of the treatment for 30 days, however, led to a surprising failure to maintain continued response. Of the 10 patients under consideration eight either failed to improve their blood picture over that of the two week determination or actually there was a decrease in almost all factors. The hemoglobin increased by a mean average of 0.012 gram, the hematocrit fell 0.21 per cent and the color index decreased 0.019 while the mean corpuscular volume fell to 76 from a previous 78. Despite these deflections in the blood values the immature forms remained at a mean average of 1.6 per cent (table 1), the monocytes remained at a mean average of 5.8 per cent, the reticulocytes were still above the initial count at 2.4 per cent and the erythrocytes exhibited no significant change.

The total alterations in the peripheral blood of the two groups of patients in one month were comparable (figures 1 and 4). The patients of Group I made a slow, steady improvement whereas those of Group II made the larger response at 14 days which was not improved but maintained at 30 days. The total hemoglobin rise in Group I was 0.87 gram, that of Group II was 0.869. The total erythrocyte count in Group I was increased by 110,000 and in Group II by 88,000. The color index had increased in both groups by the identical figure of 0.044 and the immature forms were 1.5 per cent and 1.6 per cent respectively.

An additional 30 days treatment in Group II produced a red cell of slightly larger size as evidenced by the increase in the mean corpuscular volume to a mean average of 76.4 and of slightly less hemoglobin concentration as reflected in the color index of 0.884. The hemoglobin increased 0.055 gram to a level of 12.13 grams and the total erythrocyte count rose only slightly. The reticulocytes were still above the initial value at 2.16 per cent. Immature forms appeared less frequently than in the previous determinations and were present in only 0.4 per cent (figure 2). A previously noted monocytosis was of less significance in the mean average and was only 4.1 per cent. Four patients (40 per cent) in the group were classified as failures. The remaining six patients exhibited an appreciable increase in all blood determinations save the total erythrocyte count.

Reevaluation of the results at the end of two months of treatment revealed that the rises exhibited in the various blood determinations were now appreciably higher than the initial values and that there was a parallelism between Groups I and II with no differences save those based on the higher initial values of the second group over those of the first.

In 90 days the peripheral blood picture in the 10 patients of Group II revealed a progressive rise in the previously indicated determinations. The hemoglobin rose to a mean average of 12.92 grams, an increase of 0.80 gram in the last 30 days. The erythrocytes maintained their constant mean average level of 4.72 million per cu. mm. Consequently the color index rose to a level of 0.944, a rise in one month of 0.060. The hematocrit was observed to be 38.29 per cent, an increase of 1.79 per cent, and the correlating

mean corpuscular volume also rose to 81.2, an addition of 4.8. The reticulocytes remained relatively constant at 2.25 per cent. The monocytes again increased to 6.6 per cent.

It was during this final 30 day period that the patients of this Group II, as was similarly done in Group I, were divided into successes and failures and, as noted, they comprised respectively 60 per cent and 40 per cent of the group. The four failures who had in 60 days of continued therapy shown no improvement were given 100 milligrams of folic acid daily with the results noted in figure 5. Whereas the hemoglobin, hematocrit, color index, mean corpuscular volume were steadily decreasing on the earlier dosages, increas-

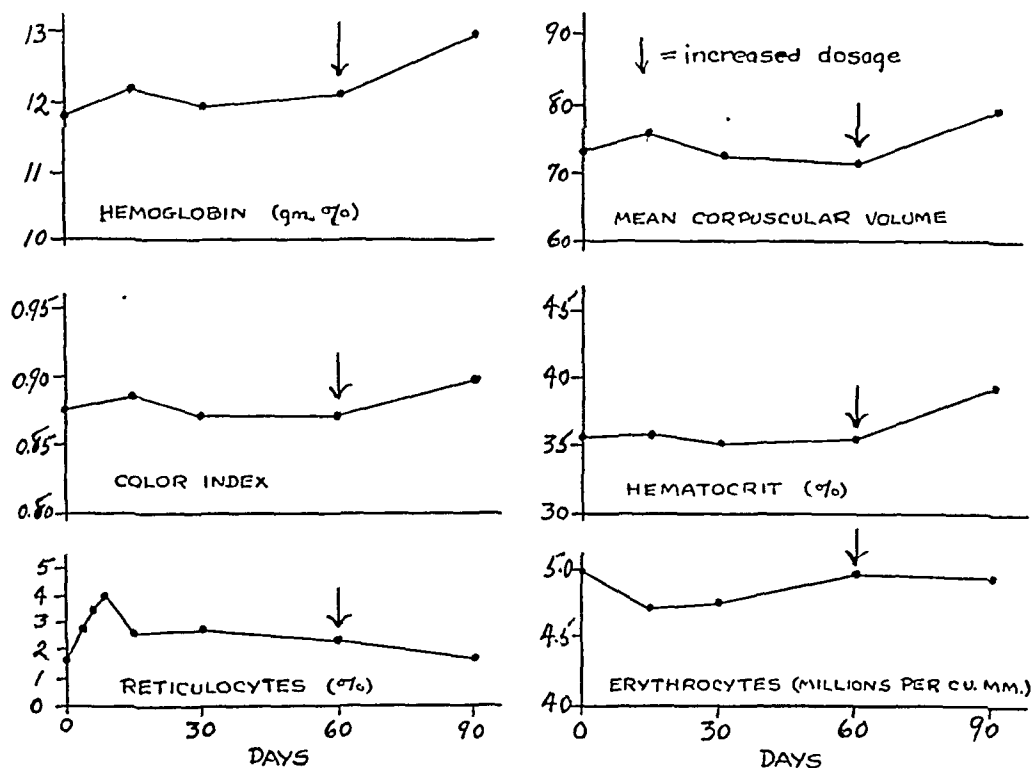


FIG. 5. Mean average blood values of 4 "failures"—Group II.

ing the dosage of folic acid without altering the dosage of iron led to improvement in each of the determined values. In all four of the unresponsive patients (figure 5) the hemoglobin rose to a mean average level of 12.98 grams, the erythrocytes remained constant, and the color index rose to 0.895. The hematocrit increased to 38.45 per cent and the mean corpuscular volume consequently rose to 78.5. The morphology of the erythrocytes revealed a diminished amount of achromia, anisocytosis, poikilocytosis, and the fragmentation was no longer so much in evidence. Immature forms also increased to 0.77 per cent (table 1) and the monocytes again appeared in increased numbers at a level of 7.8 per cent (figure 2).

Every patient classified as a "failure" was subjected to a gastric analysis

and free hydrochloric acid was demonstrated in each. In these same patients urobilinogen levels were normal.

Determinations of the sedimentation rates by means of a modified Westergren method<sup>36</sup> were performed at the intervals already indicated. No alterations beyond those normally expected were observed. Total leukocyte counts were not consistently altered nor were any other specific cells save the monocytes.

Immature cells were first observed on the fourteenth day of treatment and during subsequent examinations they appeared in the differential counts in 10 patients (100 per cent) in Group I and in eight patients (80 per cent) in Group II. Each cell was meticulously identified by means of the criteria established by Dr. Edwin E. Osgood.<sup>37</sup> They appeared at an earlier date in the treatment in Group I and were found in larger numbers than in Group II. At no time during the examinations were stem cells found but cells in all other stages of development were demonstrated. Singularly enough cells belonging to the "pro" stages were found with more frequency than the more mature young forms. Most commonly encountered were cells belonging to the granulocyte series while the prolymphocytes were observed to be next in frequency (table 1).

During this period of therapy in both groups there was a consistent and spontaneously noted generalized sense of well being. However, there was neither objectively nor subjectively any alteration in the progress of the rheumatoid arthritis nor in the degree of functional disability of the patients. No toxic manifestations, untoward effects or discomforts from the therapy were observed in any of the dosages of folic acid employed.

A few additional isolated observations were made. One patient was given 500 milligrams of folic acid per day for five days. A reticulocytosis of 11 per cent was observed on the eighth day and there was a rapid rise to a large degree in the hematocrit, the hemoglobin, the mean corpuscular volume and the color index.

Several patients were given 1.7 milligrams of folic acid daily and there was a response in each patient which was commensurate with this small dosage but which in 90 days showed an accumulative effect. One of this group was given 100 milligrams of folic acid daily for 30 days after having shown a moderate response on the small dosage of folic acid and there was a dramatic improvement in the blood picture identical with those already noted.

#### COMMENTS

With the facts at hand and the limited number of patients included in this preliminary report any comments must of necessity be of a presumptive nature. It would appear that folic acid in the dosages given exerts an effect on the anemia of rheumatoid arthritis, an effect not observed with any other hematopoietic agent. The peripheral blood picture in rheumatoid arthritis is not only that of a hypochromic, microcytic anemia but the erythrocytes

are sickly in appearance; they are variable in size and shape, stain poorly, are generally small, and have a tendency to fragment easily. Folic acid caused the erythrocytes in the treated patients to be of greater size, of more uniform appearance, of greater staining intensity, and to show less inclination to fragment. Before treatment the morphology of the erythrocytes in many instances resembled the so-called "doughnut cells" and following the use of folic acid the cells were of more uniform character and appeared more amply filled with hemoglobin.

There are no results in any way comparable to those seen in the large and dramatic response to folic acid in pernicious anemia and sprue as shown by Spies et al. On the other hand, the slow, steady, prolonged benefit exerted by folic acid in the anemia of rheumatoid arthritis cannot be disregarded.

At the end of 90 days, 100 per cent of our patients, including the failures treated with increased dosage, enjoyed an improvement in their anemia. The mean corpuscular volume, the hemoglobin, and the color index rose a statistically significant amount in all instances. Of the patients studied those with the most active and vicious rheumatoid arthritis responded poorly on the 20 milligram daily dose and they comprise the majority of the seven failures of both groups.

In our opinion the most remarkable result we encountered was the appearance of young forms in the differential counts made on the peripheral blood. This is a phenomenon not previously observed by one of us (A. B.) in 11 years of continuous observation of the peripheral blood of patients with rheumatoid arthritis under all forms of anti-anemic therapy. Of further interest is the unexplainable occurrence of more cells of the "pro" stages than of the "meta" stages.

Those patients regarded as failures on the 20 milligram daily dose of folic acid responded correspondingly well on increased dosage; which would indicate that the problem of dosage has not yet been solved. Perhaps some patients will benefit from much smaller doses than those employed in this study and we have evidence to show that others require larger amounts of the drug.

The patients of that group given both folic acid and iron did not initially have as profound an anemia as the patients given folic acid alone but the proportionate improvement was almost identical in both groups. This would signify that iron in the dosages given exerted no influence. Increase in the hemoglobin concentration of the erythrocytes was observed without the use of iron (Group I). It would seem fair to conclude, therefore, that the hypochromic anemia of rheumatoid arthritis originates from a cause not intimately associated with the ingestion of ferrous salts and further that folic acid influences this anemia by a mechanism as yet unknown.

In any group of patients with a chronic disease there may exist a simple iron deficiency anemia. Therefore we would hasten to state that iron is not

to be discarded as totally ineffectual in all patients suffering from rheumatoid arthritis. However, it would appear from our results that there is a superimposed process of hematopoietic insufficiency which is not based on inadequate iron in the diet and which does respond to folic acid.

The monocytosis has been carefully included in the reporting of the results because in the differential count that particular cell was the only one observed to undergo any percentage change. The significance of this interesting occurrence cannot be stated. The complete ineffectiveness of folic acid in influencing the underlying disease process in the time involved would suggest that the increase in the number of monocytes bears no relation to recovery or repair and that possibly this phenomenon is merely a side effect in the pharmacological action of folic acid.

The ineffectiveness of crude liver in correcting the anemia of rheumatoid arthritis and the evident benefits of folic acid appear to divorce these substances in their pharmacological action. It has been observed that liver will cause an adequate response in pernicious anemia in relapse or in sprue although assays reveal only small ineffective amounts of folic acid in the extract. The proponents for the specificity of folic acid in the treatment of macrocytic anemias suggest that there are additional liver substances which release bound or stored folic acid already in the body. Our results would tend to discredit this theory or at least suggest that there is a great variation in the effective dosages of folic acid in different diseases.

Additional studies with increased dosage are being carried out and as further light is thrown on this apparently powerful bone marrow stimulant it may be determined that folic acid will play a significant rôle as one of the multiple therapeutic agents used in the treatment of this vicious, debilitating, and disabling disease.

### CONCLUSIONS

1. Folic acid improved the blood picture in 100 per cent of a group of 20 patients with rheumatoid arthritis. There was an increase in the mean corpuscular volume, the hematocrit, the hemoglobin, the color index, and the morphology of the erythrocytes without comparable rise in the total erythrocyte or leukocyte counts.
2. Folic acid caused the appearance in the peripheral blood of immature leukocytes and erythrocytes of all categories save those of the plasmacyte series, a phenomenon heretofore not noted with any other antianemic therapy in rheumatoid arthritis.
3. Iron did not enhance or detract from the hematinic effectiveness of folic acid in those patients studied.
4. Folic acid produced an appreciable monocytosis.
5. No improvement was noted in the underlying disease, rheumatoid arthritis, nor were any toxic manifestations observed in any of the dosages employed.

6. The dose of folic acid required to produce a response apparently varies widely.

#### BIBLIOGRAPHY

1. PEMBERTON, RALPH: A few simple recommendations to the general practitioner in his care for arthritics, *Illinois Med. Jr.*, 1936, lxx, 479-483.
2. PAINTER, C. F.: Importance of early diagnosis and careful differentiation of types of chronic arthritis, *New Eng. Jr. Med.*, 1933, ccviii, 447-450.
3. SMITH, M.: A study of 102 cases of atrophic arthritis. Introduction: Statistical data, *New England Med. Jr.*, 1932, ccvi, 103-110; Constitutional defects, 1932, ccvi, 160-173; Etiologic factors, 1932, ccvi, 211-216.
4. MINOT, G. R.: Chronic arthritis; remarks concerning prevention and treatment, *Med. Clin. N. Am.*, 1932, xv, 797-804.
5. HENCH, P. S.: Effect of jaundice on chronic infectious (atrophic) arthritis and on primary fibrositis; further observations; attempts to reproduce the phenomenon, *Arch. Int. Med.*, 1938, lxi, 450-480; 495-500.
6. HENCH, P. S.: The effect of spontaneous jaundice on rheumatoid (atrophic) arthritis; attempts to reproduce the phenomenon by various means including "artificial jaundice" (induced hyperbilirubinemia), *Brit. Med. Jr.*, 1938, ii, 394-398. Also in: *Proc. of the International Congress on Rheumatism and Hydrology (London and Oxford) and the Bicentenary Congress on Chronic Rheumatism (Bath)*, March 25th to April 2nd, 1938, Healdy Brothers, London, pp. 315-331.
7. HENCH, P. S.: The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis, *Proc. Staff Meet. Mayo Clin.*, 1938, xiii, 161-167.
8. COLLINS, D. H.: Observations on the anemia in chronic rheumatic disease, *Lancet*, 1935, ii, 548-550.
9. BREUER, M. J.: Chronic infectious arthritis, *Nebraska State Med. Jr.*, 1938, xxiii, 361-365.
10. GRAY, J. W., BERNHARD, W. G., and GOWEN, C. H.: Clinical pathology of rheumatoid arthritis, *Am. Jr. Clin. Path.*, 1935, v, 489-503.
11. HENCH, P. S.: Rheumatism reviews, *Ann. Int. Med.*, 1940, xiii, 1655, 1837.
12. HOLBROOK, W. P.: The management of atrophic arthritis in relation to the different phases of the disease, *Proc. Am. Assoc. for the Study and Control of Rheumatic Diseases*, June 11, 1934.
13. HOLBROOK, W. P., and HILL, D. F.: Treatment of atrophic arthritis, *Jr. Am. Med. Assoc.*, 1936, cvii, 34-38.
14. IRONS, E. E.: Chronic arthritis, a generalized disease requiring individual treatment, *Ann. Int. Med.*, 1936, ix, 1658-1663.
15. HOLBROOK, W. P.: Evaluation of therapy in chronic atrophic arthritis, *Ann. Int. Med.*, 1933, vii, 457.
16. DOUTHWAITE, A. H.: The pharmacology of chronic rheumatism. In a survey of chronic rheumatic diseases, 1938, Oxford University Press, London, pp. 265-275.
17. CECIL, R. L.: Textbook of medicine, Fifth Edition, 1940, W. B. Saunders Co., Philadelphia and London, p. 1412.
18. Cushny's Pharmacology and therapeutics, C. W. Edmunds and J. A. Gunn, Eleventh Edition, 1938, Lea and Febiger, Philadelphia.
19. HARTUNG, E. F.: The treatment of chronic rheumatism, *Trans. Am. Therapy Soc.*, 1938, xxxviii, 30-37.
20. HADEN, R. L.: Rheumatoid arthritis; etiology and treatment, *Arch. Phys. Therapy*, 1940, xxi, 671-677.
21. FARRAR, G. E., JR., and RAYBURN, F. W.: The blood in arthritis, *Med. Clin. N. Am.*, 1940, xxiv, 1633-1645.

22. COPEMAN, W. S. C.: Treatment of rheumatism in general practice, 1933, William Wood and Company, Baltimore, p. 215.
23. SPIES, T. D.: Effect of folic acid on persons with macrocytic anemia in relapse, Jr. Am. Med. Assoc., 1946, cxxx, 474.
24. SPIES, T. D., VILTER, C. F., KOCH, M. B., and CALDWELL, M. H.: Observations on the anti-anemic properties of synthetic folic acid, South. Med. Jr., 1945, xxxviii, 707.
25. VILTER, C. F., SPIES, T. D., and KOCH, M. B.: Further studies on folic acid in the treatment of macrocytic anemias, South. Med. Jr., 1945, xxxviii, 781.
26. MOORE, C. V., BIERBAUM, O. S., WELCH, A. D., and WRIGHT, L. D.: The activity of synthetic *Lactobacillus casei* factor ("folic acid") as an antipernicious anemia substance. I. Observations on 4 patients: 2 with Addisonian pernicious anemia, one with nontropical sprue and one with pernicious anemia of pregnancy, Jr. Lab. and Clin. Med., 1945, xxx, 1056.
27. DARBY, W. J., JONES, EDGAR, and JOHNSON, H. C.: The use of synthetic *L. casei* factor in the treatment of sprue, Science, 1946, ciii, 108.
28. SPIES, T. D., LOPEZ, GUILLERMO GARCIA, MENENDEZ, JOSE A., MINNICH, VIRGINIA, and KOCH, MARY B.: The effect of folic acid on sprue, South. Med. Jr., 1946, xxxix, 30.
29. SPIES, T. D., MILANES, F., MENENDEZ, A., KOCH, MARY B., and MINNICH, V.: Observations on the treatment of tropical sprue with folic acid, Jr. Lab. and Clin. Med., 1946, xxxi, 227.
30. MILLS, R. C., BRIGGS, G. M., JR., ELVEHJEM, C. A., and HART, E. B.: *Lactobacillus casei* factor in nutrition of the chick, Proc. Soc. Exper. Biol. and Med., 1942, xlix, 186.
31. WATSON, C. J., SEBRELL, W. H., MCKELVEY, J. L., DAFT, F. S., and HAWKINSON, V.: Possible effectiveness of the *L. casei* factor (folic acid) concentrate on the refractory anemia and leukopenia following radiation therapy, Am. Jr. Med. Sci., 1945, ccx, 463.
32. HASKINS, H. D., and OSGOOD, E. E.: Methods of estimating hemoglobin (Haskins-Sahli), Northwest Med., 1926, xxv, 500-503.
33. PHILLIPS, R. A., VAN SLYKE, D. D., DOLE, V. P., EMERSON, K., JR., HAMILTON, P. B., and ARCHIBALD, R. M., with the technical assistance of STANLEY, E. G., and PLAZIN, J.: The copper sulfate method for measuring specific gravities of whole blood and plasma, Monograph, New York, 1943; Bull. U. S. Army Med. Dept., 1943, lxxi, 66.
34. OSGOOD, E. E., and WILHELM, MABLE M.: Reticulocytes, Jr. Lab. and Clin. Med., 1934, xix, 1120-1135.
35. WESTERGREN, A.: Technic of red cell sedimentation reaction, Am. Rev. Tuberc., 1926, xiv, 94-101.
36. OSGOOD, E. E.: Modified Westergren method, laboratory diagnosis, Third Edition, The Blakiston Company, Philadelphia.
37. OSGOOD, E. E., and ASHWORTH, C. M.: Atlas of hematology, J. W. Stacey, Inc., San Francisco.

## THE HEART RATE IN MALARIA; A REVIEW OF NINETY CASES \*

By SHERMAN M. MELLINKOFF, Capt., M.C., A.U.S., and JOHN R. HIGGINS, Capt., M.C., A.U.S.

MOST textbooks state that the typical malaria patient exhibits chills, fever, and tachycardia.<sup>1, 2, 3, 4, 5</sup> This clinical triad is frequently helpful in the differential diagnosis that runs through the physician's mind when he first sees a patient in a malarious zone. Among army personnel in certain regions of Asia, for example, it is common to see an acutely ill, prostrated man with chills and fever, while the physical examination gives no clue to the diagnosis except the heart rate. On the basis of probability in this particular locality, when there is a relative bradycardia one thinks of the pre-icteric stage of hepatitis first and typhoid fever second. In both of these diseases the white count is ordinarily low. At an Asiatic military hospital we have been occasionally surprised, however, to find that a patient with fever, relative bradycardia, and leukopenia turns out to be ill with malaria.

Bradycardia is not usually considered to be a feature of malaria, although some investigators have pointed out this important phenomenon.<sup>6, 7, 8</sup> Indeed Hughes and Bomford maintain that "relative bradycardia was a principal feature of the disease (malaria) as seen by us in West Africa."<sup>9</sup> The British Army considers that "malaria may simulate any acute or subacute fever and may be called on this account 'The Great Mimic' among diseases."<sup>10</sup>

We have reviewed the records of our malaria patients to investigate the relationship between pulse rate and fever. Our findings indicate that the pulse rate covers a wide latitude in malarial fevers, and ranges from the tachycardia seen in the ordinary septic diseases to the bradycardia of typhoid.

All patients definitely diagnosed as malaria during the months of January through the first part of September, 1946, are included in the present study, with the exception of four patients with falciparum malaria whose charts were lost to us through transfer to a higher echelon. In all 90 cases the diagnosis was made by identifying the parasite in thin or thick blood smear. There were 85 patients with *Plasmodium vivax*, two with *Plasmodium falciparum*, and three with *Plasmodium malariac*. Most of the infestations were traceable to the Philippine Islands, the appearance of clinical symptoms having been delayed by prophylactic doses of atabrine. The latter were discontinued at various times ranging from September, 1945, to April, 1946. One patient with quartan malaria contracted the disease in Okinawa, and six cases were acquired in Korea—two due to each of the three types of plasmodia. The remainder of the cases were contracted in the Philippine Islands.

\* Received for publication November 22, 1946.



RELATIONSHIP BETWEEN PULSE AND FEVER  
IN NINETY CASES OF MALARIA

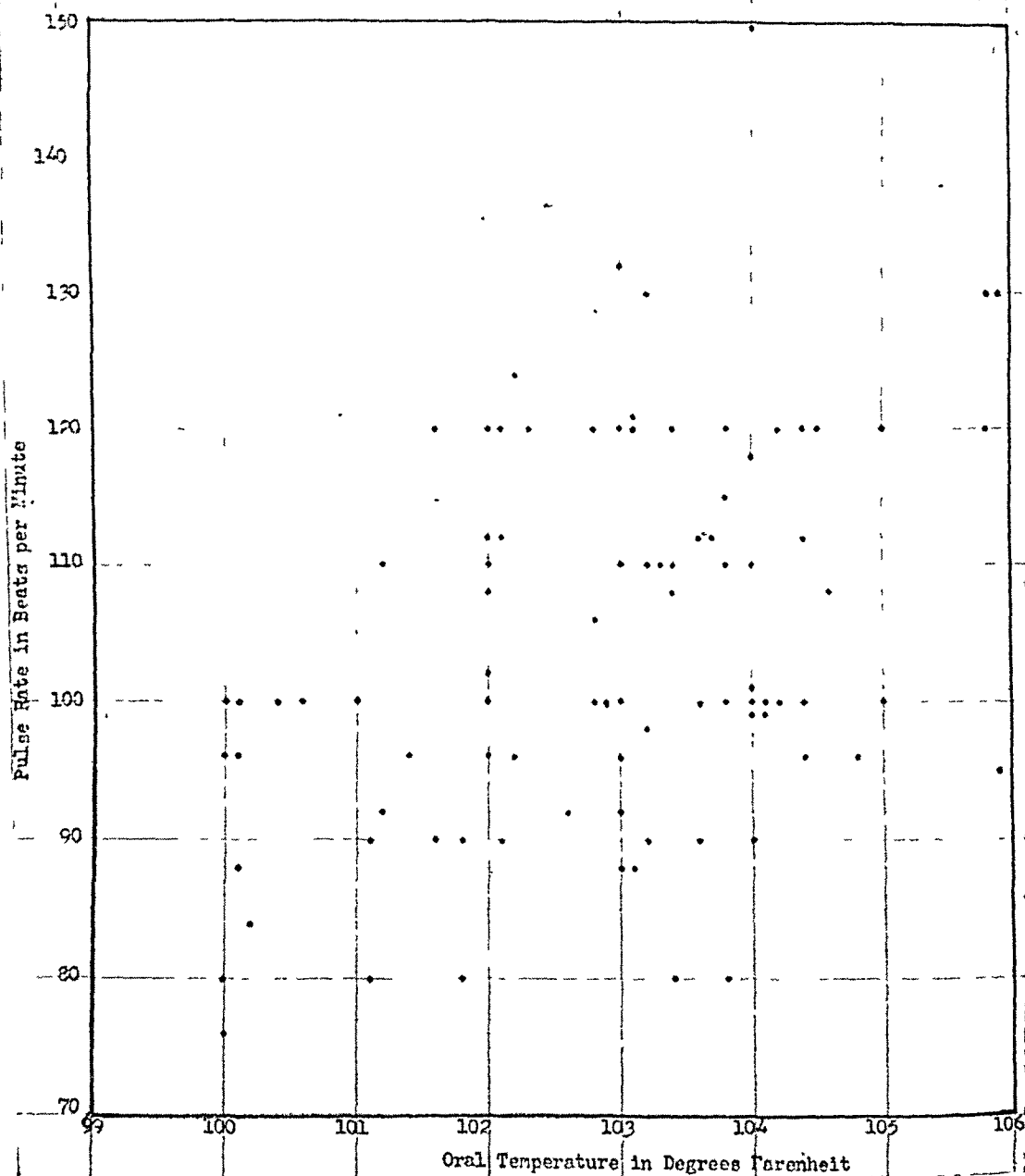


FIG. 1.

Most of the patients had at least one full-blown chill in the hospital before the diagnosis was made. A few were admitted in the decline of an initial chill, and diagnosis was made and therapy instituted before a second chill made its appearance. Since this paper is primarily concerned with the clinical picture of the patient when first seen by the doctor, the relationship between the highest fever and the highest pulse rate on the first hospital day is

recorded. These peaks represent the height of a malarial paroxysm in the majority of patients. In some they represent a fever seen at some time during the subsidence of a paroxysm. About one fourth of the patients, however, had two or more chills in the hospital. An analysis of those chills indicates that the data contained here are not artefacts created by the in-

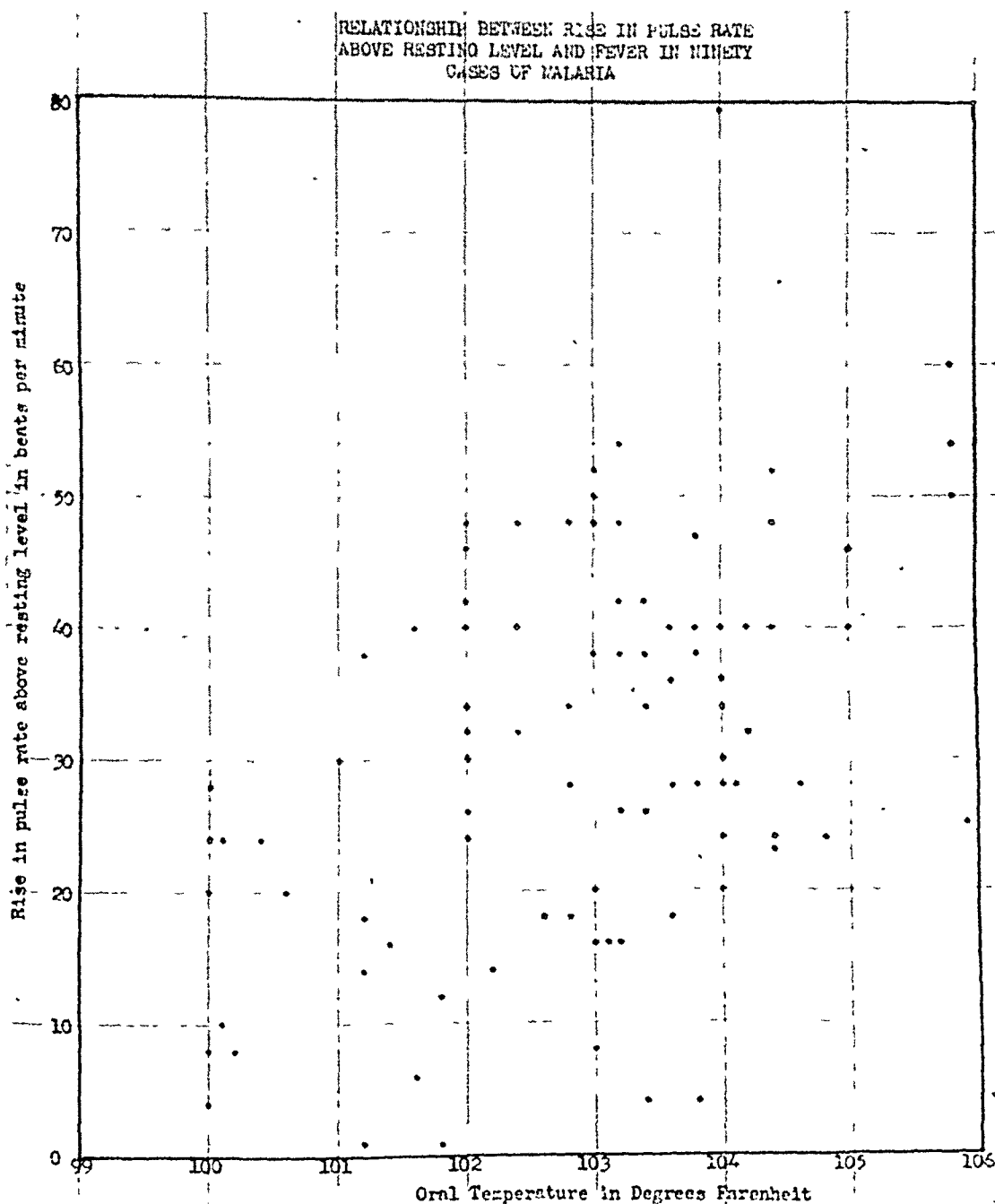


FIG. 2.

cidents of hospital admission, but rather are characteristic of all paroxysms observed.

There were no deaths or permanent disabilities. All patients were treated with atabrine alone, or atabrine in conjunction with quinine. In 13 patients there was an associated disease, but in no case was the secondary illness of a type or severity to change substantially the temperature and pulse. Examples are coryza, ascariasis, and non-specific penile ulcer.

One patient was 31 years of age, and the others were from 18 to 24 years old. In eight cases there was no chill, although in these eight cases the ob-

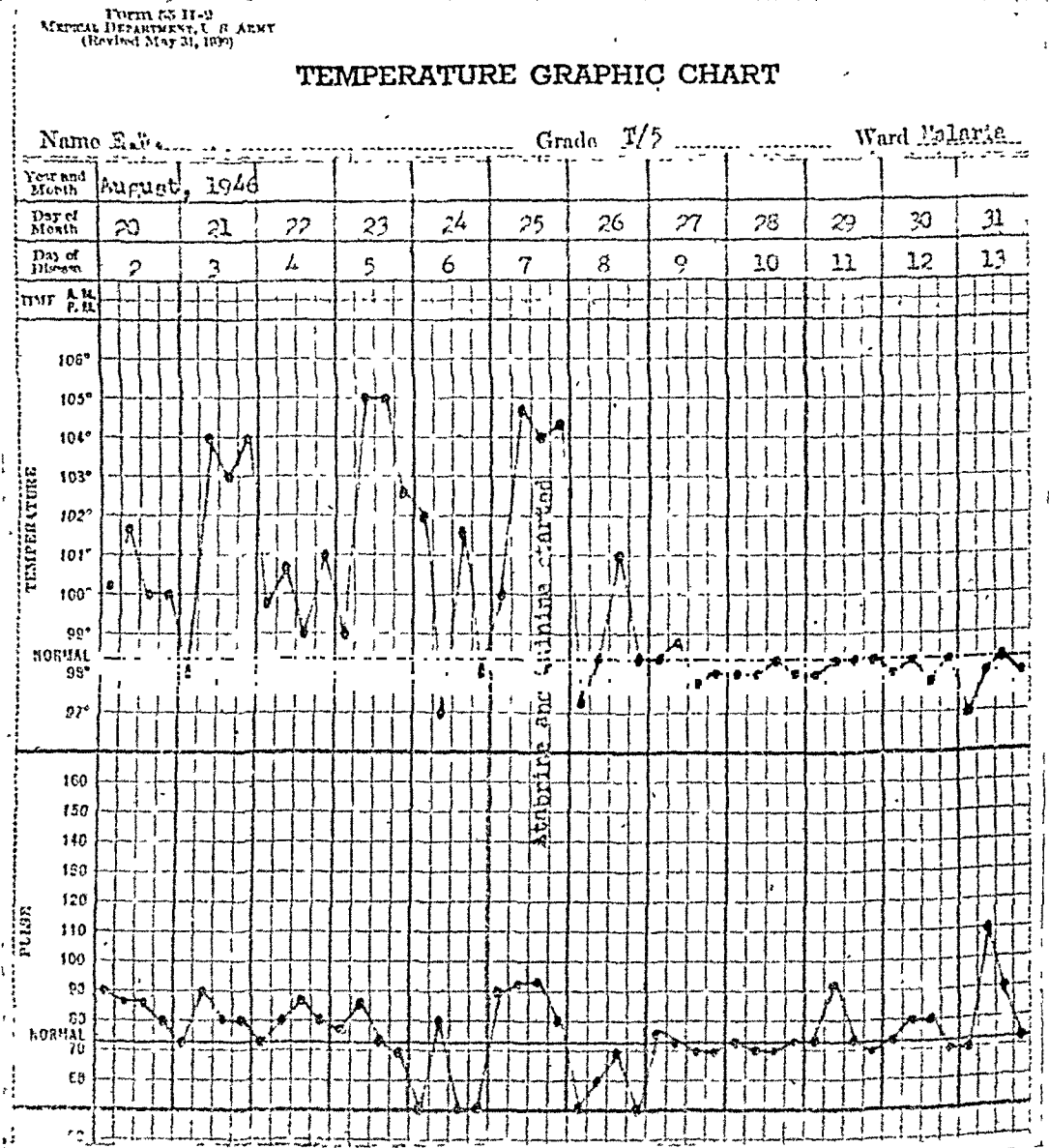


FIG. 3.

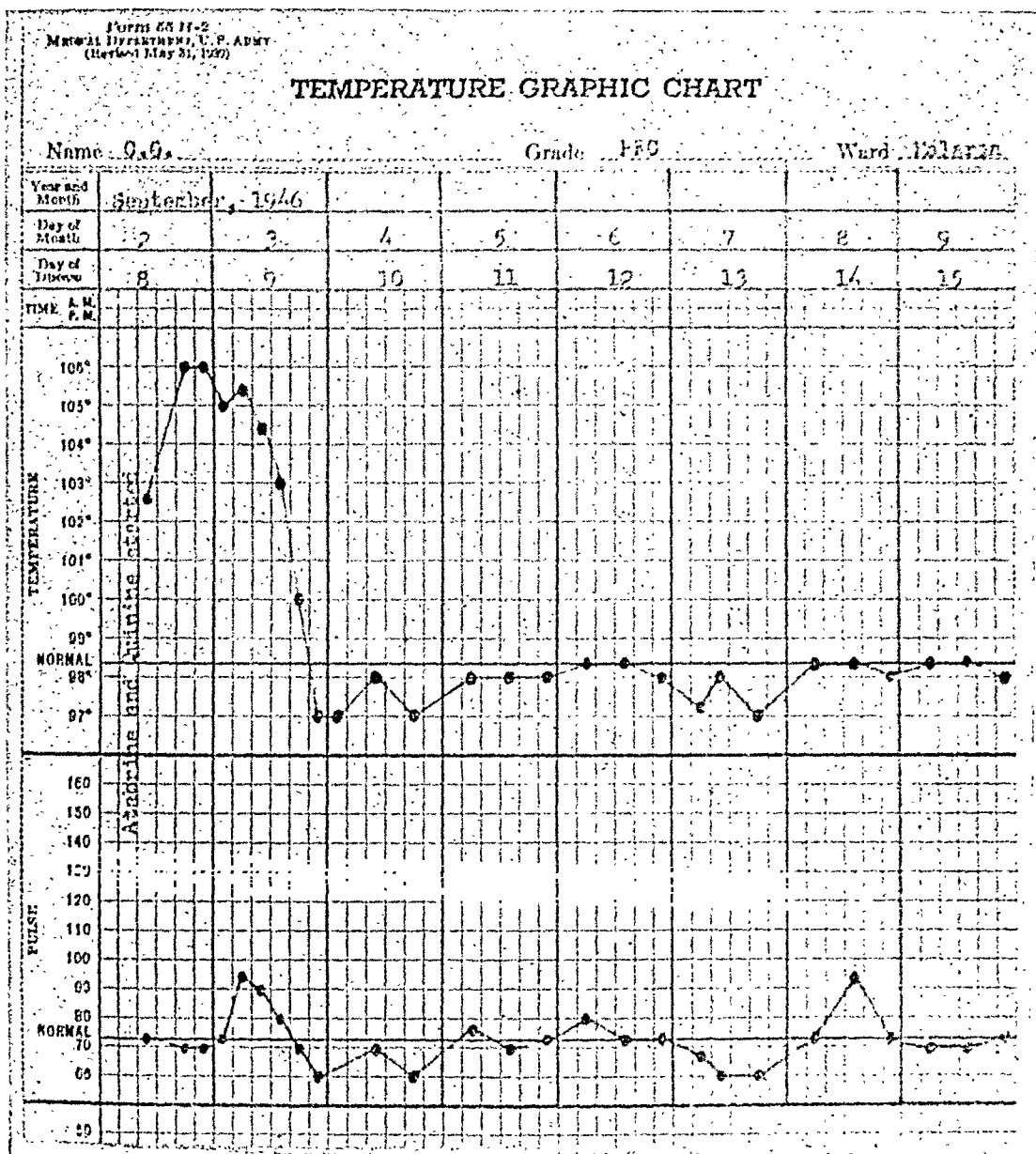


FIG. 4.

served fever ranged from 102.8 to 104° Fahrenheit by mouth. In 29 patients the degree of malaise was surprisingly mild. These men would complain of "feeling hot," and almost only if specifically asked would admit "a little headache" and "a few aches in the bones." The remaining 61 patients had varying degrees of more severe malaise. One of the cases of falciparum malaria had extreme prostration, a pounding headache, photophobia, pronounced nuchal rigidity, lancinating pains in the thighs, a feeling of impending death, and marked irascibility. Examination of his spinal fluid was negative. Thirty-nine patients complained of nausea, and 14 of those had

more or less severe vomiting. One of the malignant tertian cases had severe hematemesis. Five patients had diarrhea, one with 20 bowel movements a day, that cleared with antimalarial therapy alone. No parasites were found in the stools, and stool culture was negative in every instance. The distribution of the white blood cell counts was as follows: (1) Between 2900 and 5000: 12 patients. (2) Between 5000 and 9000: 39 patients. (3) Between 9000 and 12,000: six patients. In the remainder no white blood count is recorded. The differential white counts were usually within normal limits, with an occasional eosinophilia, an occasional relative lymphocytosis or monocytosis, and rarely a relative preponderance of polymorphonuclear leukocytes.

TABLE I  
Relationship between Pulse and Fever in 90 Cases of Malaria

Temp.	Number of patients with pulse rate of						No. patients with rise above resting pulse of					
	70-80	81-90	91-100	101-110	111-120	121-150	0-10	11-20	21-30	31-40	41-50	51-80
100-100.9	2	2	6	0	0	0	.4	2	4	0	0	0
101-101.9	2	3	3	1	1	0	3	4	1	2	0	0
102-102.9	0	1	6	4	6	1	0	3	4	6	5	0
103-103.9	2	4	6	6	7	3	3	5	4	8	6	2
104-104.9	0	1	8	3	5	1	0	1	8	6	1	2
105-106	0	0	2	0	2	2	0	0	1	1	2	2

Number of patients with temperature above 102.9 and pulse below 101.....23 or 25.5%

Number of patients with temperature above 102.9 and pulse below 91..... 7 or 7.7%

Number of patients with temperature above 102.9 and pulse-rise above resting level of less than 31.....22 or 24.4%

Number of patients with temperature above 102.9 and pulse-rise above resting level of less than 21.....10 or 11.1%

By reference to the accompanying graphs and table one can observe the degree of cardiac acceleration in relation to the fever. The pulse recordings represent the greatest relative tachycardia observed with the height of each initial fever. After subsidence of all fever and malaise, the resting pulse rate was determined in each case by observing the consistent pulse rate an hour after the patient had awakened after a good night's sleep. The interval hour comprised bed rest. In the second graph the height of each fever is plotted against the maximum rise above the resting pulse rate in each case. By comparing the two graphs it can be seen that the degree of tachycardia or relative bradycardia was not a factor of the resting pulse rate, but indeed represented

a true variation in the cardiovascular response to fever. The variation was very wide and indicates that tachycardia as well as relative bradycardia can occur.

To illustrate the instances of relative bradycardia the temperature and pulse graphs of two patients are presented:

Patient "E. W." was a 20 year old white infantryman who entered the hospital on August 20, 1946 complaining of fever, lassitude, headache, and "dizziness" of 24 hours' duration. Onset had been gradual, and there were no chills. Physical examination was entirely negative except for the fever. Blood pressure was 120 mm. of mercury systolic and 60 diastolic. White blood cell count was 2900, with 68 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, and 7 per cent monocytes. The pulse rate at no time rose above 91, while three tertian fevers were observed, reaching respectively 104, 105, and 104.8° Fahrenheit by mouth. It was interesting that when the patient was afebrile and his activity confined to lavatory privileges, there was as much rise in pulse rate as there was with the fever. *Plasmodium vivax* was discovered in thin blood smear during the third paroxysm, and routine anti-malarial therapy was instituted. On the twelfth hospital day the following observations were made: When the patient stepped off and on a chair 16 inches high 15 times in four minutes the pulse rate rose from 72 to 118 beats per minute. When this procedure was carried out 20 times in eight minutes, the pulse rate rose from 72 to 122 beats per minute. In short, a relatively small amount of exercise was capable of producing a greater cardiac acceleration than was a fever of 105°.

Patient "C. G." was a 19 year old white private in the military police. One week prior to admission he had developed a pounding occipital headache and stiffness in the neck. Five days before admission he had a severe chill with shivering and generalized malaise. This was followed in four hours by a profuse diaphoresis. In the following five days he had a similar paroxysm every day, and on the eighth day of his illness he was admitted to the hospital just after a relatively mild chill. Physical examination was entirely negative except for fever and prostration. Blood pressure was 120 mm. of mercury systolic and 50 diastolic. Blood smear immediately revealed typical quartan parasites and atabrine and quinine were given at once. One half hour later the patient had a second chill, with shaking and severe headache. By reference to the temperature graph it can be seen that when the fever was 106° the pulse rate was 70, while the height of the pulse rate was only 95 with a fever of 105.4°. On the eighth hospital day the patient rested two hours in bed and then stepped on and off a chair 16 inches high 15 times in four minutes. The pulse rate rose from 70 to 115 beats per minute.

### SUMMARY AND CONCLUSIONS

1. Ninety cases of malaria are reviewed with particular attention to the relationship between pulse rate and fever.

2. Malarial fevers may be accompanied by all degrees of cardiac acceleration, ranging from the tachycardia seen in many bacterial infections to the bradycardia of typhoid fever.

3. In this series of cases about one fourth of the patients had a relative bradycardia.

## BIBLIOGRAPHY

1. STRONG, R.: Stitt's Diagnosis, prevention and treatment of tropical diseases, 1944, Blakiston Co., Philadelphia, pages 67 and 77.
2. NAPIER, L. E.: The principles and practice of tropical medicine, 1946, Macmillan Co., page 81.
3. MANSON-BAHR, P. H.: Tropical diseases, 1945, Cassell and Co., Ltd., London, page 67.
4. MACKIE, T. T., HUNTER, G. W., and WORTH, C. B.: Manual of tropical medicine, 1945, W. B. Saunders Co., Philadelphia, page 243.
5. CRAIG, C. F., and FAUST, E. C.: Clinical parasitology, 1940, Lea and Febiger, Philadelphia, page 206.
6. JONES, A. N.: Malignant malaria on the gold coast, *Ann. Trop. Med.*, 1944, xxxviii, 2.
7. NOEHREN, T. H.: The malaria triad, *Ann. Int. Med.*, 1946, xxiv, 299.
8. HYMAN, A. S.: Clinical masquerades of malaria, *U. S. Nav. Med. Bull.*, 1945, xlv, 297.
9. HUGHES, S. B., and BOMFORD, R. R.: Clinical features and treatment of malaria in British troops in West Africa, *Brit. Med. Jr.*, 1944, i, 71.
10. The War Office Memoranda on Medical Diseases in Tropical and Subtropical Areas, 1942, Chemical Publishing Co., London.

# CASE REPORTS

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## AN UNUSUAL CASE OF VENTRICULAR TACHYCARDIA \*

By S. DEMAREST BEERS, M.D., and CLARENCE E. DE LA CHAPELLE, M.D.,  
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### CASE REPORT

A 57 year old white male was admitted to this hospital with the chief complaint of palpitation of 10 hours' duration.

The patient gave a history of attacks of palpitation for some 20 years lasting from a few minutes to a few hours. They were accompanied by weakness and dyspnea. The interval between the attacks varied from one to six months. The attacks were apparently initiated by over-eating and excitement. During the year prior to admission he had two or three episodes which lasted for 24 hours or longer. The attacks usually began and ended abruptly and spontaneously. Frequently he was able to terminate the attacks by stretching his arms and twisting his body. Carotid sinus pressure or orbital pressure was never tried.

He gave no history of chest pain, exertional dyspnea, orthopnea, nocturnal paroxysmal dyspnea or peripheral edema. No history of rheumatic fever or heart disease could be elicited.

The patient was seen in the Cardiac Clinic 12 days prior to his present attack of palpitation at which time his blood pressure was 196 mm. Hg systolic and 108 mm. diastolic. There was a short, low-pitched systolic murmur audible at the apex; the rhythm was regular with occasional premature contractions. An electrocardiogram taken February 26, 1945 (figure 1), about three weeks before the present episode, showed  $T_1$  and  $T_2$  diphasic,  $P_2$  and  $P_3$  notched, and a rate of 75 per minute.

His present attack of palpitation began 10 hours prior to admission and could not be terminated by him.

*Physical examination* on admission March 17, 1945. Temperature 100.4° F., respirations 24; pulse 144; blood pressure 110 mm. mercury systolic and 80 mm. diastolic.

He appeared dyspneic and slightly cyanotic. An injected pharynx was noted. Wheezes and rhonchi were heard throughout both lung fields and some moist râles at both bases. The point of maximal impulse was in the fifth left intercostal space, midway between the anterior and mid-axillary lines. No thrills were palpable. The heart sounds were of good quality, and no murmurs were heard; ventricular rate was 200; pulse rate, 168. The liver was palpable one finger's breadth below the right costal margin. There was no peripheral edema.

*Laboratory data:* Hemoglobin 12.0 gm. Red blood cell count was 3,900,000. White blood cell count was 9000 with polymorphonuclears 72 (15 immature), and lymphocytes 28. Wassermann reaction was negative. Urinalysis showed a trace of albumin and four to six white blood cells per high power field. The erythrocyte sedimentation rate was 6.0 mm. in one hour.

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From Lenox Hill Hospital, New York, N. Y.



An electrocardiogram (figure 2) taken on the day of admission (March 17, 1945) showed ventricular tachycardia with a rate of 160,  $T_1$  inverted,  $Q_2$  and  $Q_3$  deep, and a left axis deviation. For the first two days he received 0.4 gm. quinidine sulfate per os every two hours for a total of 5.4 gm. Despite this the ventricular tachycardia of 160 persisted. On the afternoon of the second day he was given 10.0 c.c. of 10 per

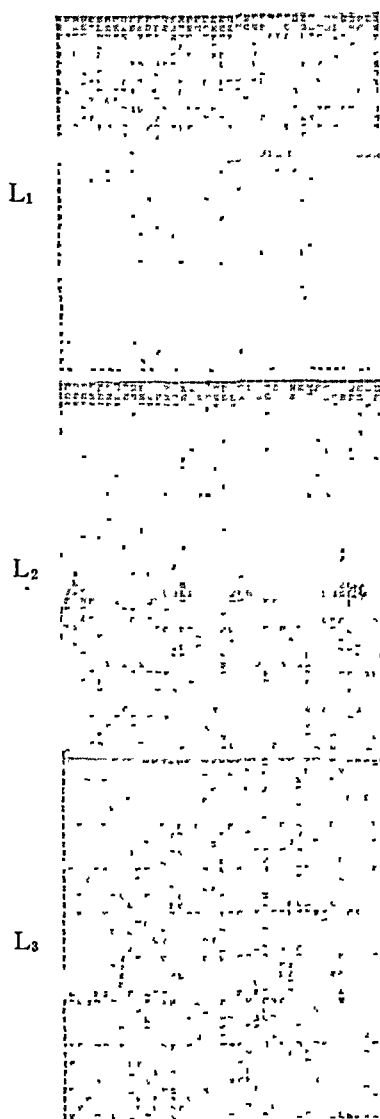


FIG 1. Electrocardiogram taken February 26, about three weeks before attack.

cent magnesium sulfate intravenously but there was no change in the rate. That same evening 20.0 c.c. of 10 per cent magnesium sulfate were repeated but with no effect. During his third and fourth hospital days the patient received 1.0 gm. potassium chloride by mouth every two hours for a total dose of 8.0 gm. On the third day, together with the potassium chloride, he received 20.0 c.c. of 25 per cent magnesium sulfate intravenously, but the ventricular rate remained at 185. On the fourth day his ventricular rate fell to 124 but rose to 168 that same day. Electrocardiograms taken on these two days were similar to the tracing taken on admission. After his

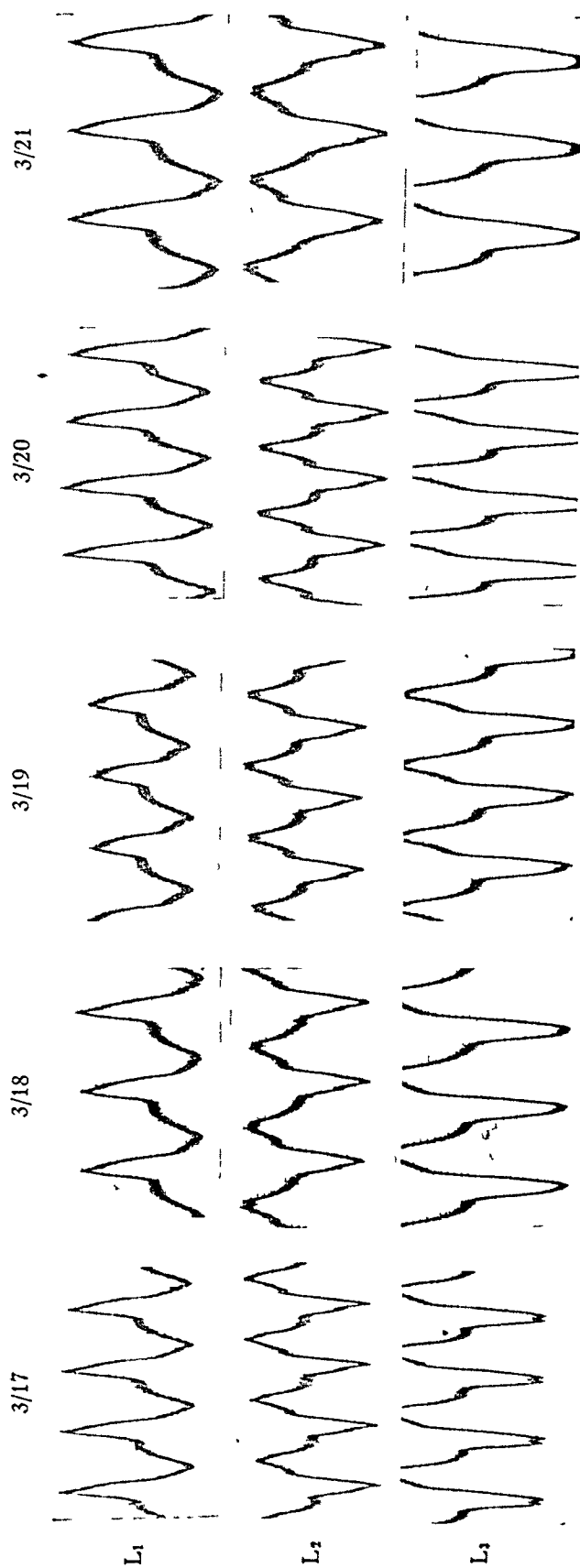


FIG. 2. Electrocardiograms taken on day of admission and on successive days, showing ventricular tachycardia.

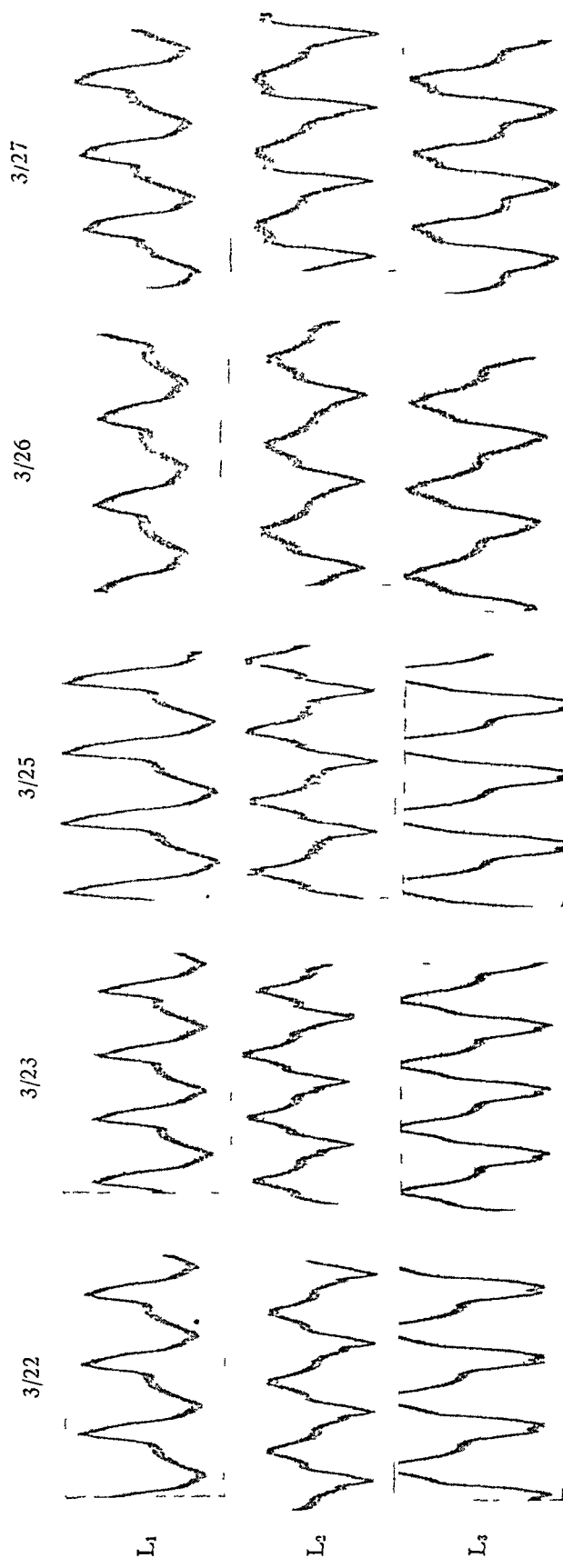


Fig. 3. Successive electrocardiograms during persistence of the attack. Ventricular tachycardia still present.

last dose of potassium chloride he was put back on quinidine sulfate, 0.6 gm. every two hours. This was continued until the afternoon of the fifth day when it was discontinued because of tinnitus and dizziness. At this time he had received a total of 7.5 gm. of quinidine sulfate, but the ventricular tachycardia persisted. For the rest of the day and the morning of the sixth day he again received 1.0 gm. potassium chloride every two hours for a total of 6.0 gm. On the sixth day the erythrocyte sedimentation rate was 42 mm. in one hour; the white blood cell count was 8000 with polymorphonuclears 72 (11 immature); lymphocytes 22; monocytes 4; and eosinophiles 2.

On the afternoon of the sixth day it was decided to give him quinidine intramuscularly as suggested by Riseman, and associates.<sup>1,2</sup> The first dose of 0.45 gm. (3.0 c.c.) was given at 3 p.m. when the heart rate was 160. At 5:30 p.m. the rate was 158 and since no toxic symptoms had developed a second dose of 0.3 gm. (2.0 c.c.) was given but without effect on the rate. On the seventh day it was decided to give him an intensive course of quinidine intramuscularly. Accordingly he was given a total of 2.75 gm. in doses of 0.45 gm. (3.0 c.c.) at intervals of approximately two hours. During this time the rate dropped to 122 but an electrocardiogram (March 22, 1945) showed that ventricular tachycardia persisted (figure 3). At the request of a member of the attending staff 1.0 c.c. of eutonon was given intravenously at 5:45 p.m. but with no effect (March 23, 1945, figure 3).

During the first week the patient's temperature per rectum showed daily fluctuations from 98.8° to 100.4° F. with a spike to 101.0° on the fourth day and another of 102.2° on the seventh. His respirations varied from 18 to 32. The pulse deficit varied from 10 to 62 beats per minute.

Throughout the eighth day the intramuscular use of quinidine was continued since no signs of cinchonism had developed. He received 4.75 gm. of quinidine during the day and that night had two doses of atropine 0.4 mg. each. His rate dropped to 120, rose to 158, and again fell to 120, but the ventricular tachycardia persisted. On the ninth and tenth days he received quinidine intramuscularly in total daily doses of 4.0 gm. and 6.75 gm. during which time the ventricular rate fell to 100. Ventricular tachycardia persisted according to an electrocardiogram taken at this time (March 25, 1945, March 26, 1945, figure 3). Toward the end of the tenth day signs of cinchonism appeared and therapy was discontinued. On the eleventh day Eutonon was again used at the request of one of the attending staff. Two doses of 2.0 c.c. each were given intravenously at 3 p.m. and at 5:30 p.m. but without any effect (March 27, 1945, figure 3). On the twelfth day the ventricular rate was 164 at 8:50 a.m. but at 10:15 a.m. it was found to be 96. An electrocardiogram revealed a normal sinus rhythm, rate 100 per minute (figure 4).

During the second hospital week minimal signs of cardiac failure developed in the form of moist râles at both lung bases. This was controlled by two intravenous injections of mercupurin at three day intervals. Four times during the first two weeks of hospital stay the patient had to be catheterized. This was attributed to the fact that the patient was on complete bed rest and had benign prostatic hypertrophy. During the second week the temperature remained below 100.0° F. except for a single spike to 102.6° on the eleventh hospital day. Respirations varied between 18 and 28.

For the next 16 days he continued to have a normal sinus rhythm with a ventricular rate that varied between 66 and 84. Respirations were normal and the temperature was never above 99.6° F. per rectum. The white blood cell count varied between 6300 and 9000 with a normal differential. The erythrocyte sedimentation rate reached a peak of 100 mm. in one hour by the twenty-second hospital day. Physical examination during this time was negative except for pulmonary rhonchi and wheezes. On the twenty-eighth hospital day and 17 days after the tachycardia had ceased, ventricular premature contractions were observed, and the patient was

put on quinidine sulfate 0.2 gm. three times a day per os. Two days later, shortly after midnight, ventricular tachycardia recurred and persisted for 30 hours during which time he received quinidine sulfate 0.2 gm. three times a day per os. The next morning the ventricular rate dropped to 90 with a normal sinus rhythm. Following this attack the dose of quinidine sulfate was increased to 0.2 gm. four times a day per os.

For the next five days the patient was asymptomatic and was allowed to sit up. On the thirty-fifth hospital day ventricular premature contractions were again noted and about 10:30 p.m. that night the patient noticed the onset of tachycardia. The next day he received 0.2 gm. of quinidine after which all medication was discontinued.

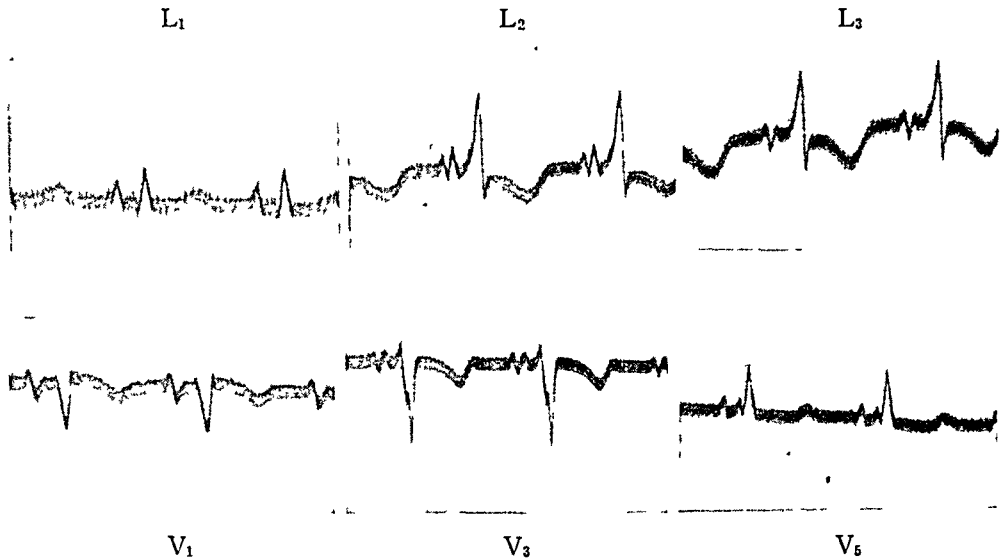


FIG. 4. Electrocardiogram taken on March 28, during an interval between attacks of tachycardia.

Twenty-six hours after the onset of this attack the rate dropped to 70 and became slow and regular. No electrocardiogram could be taken during this attack owing to mechanical difficulty. Following this episode the patient was allowed up gradually and finally discharged 40 days after admission.

Electrocardiograms taken between the three short episodes of tachycardia showed notching of P in the standard leads as well as depression of the ST segment and diphasic T waves in Leads II and III (figure 4). These T waves gradually became upright, but the pattern was repeated after each bout of tachycardia (figure 3).

The patient was considered to have sustained a coronary occlusion with myocardial infarction. For this reason the intravenous use of either quinine or quinidine was avoided because of a previous unfortunate experience some years ago on the part of one of us (C. E. C.) and despite more recent reports of favorable responses.<sup>3</sup>

### SUMMARY

An unusual case of ventricular tachycardia is reported which persisted for 12 days in spite of intensive therapy and which had a spontaneous return to normal sinus rhythm. The underlying structural disease was considered to be myocardial infarction.

## BIBLIOGRAPHY

1. STURNICK, M. I., RISEMAN, J. E. F., and SAGALL, E. L.: Intramuscular quinidine in cardiac arrhythmias, Jr. Am. Med. Assoc., 1943, cxxi, 917.
2. RISEMAN, J. E. F., and LINENTHAL, H.: Paroxysmal ventricular tachycardia, Am. Heart Jr., 1941, xxii, 219.
3. HEPBURN, J., and RYKERT, H. E.: Use of quinidine sulfate intravenously in ventricular tachycardia, Am. Heart Jr., 1937, xiv, 620.

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## SO-CALLED "INFARCTION TYPE" ELECTROCARDIOGRAPHIC CHANGES FOLLOWING PAROXYSMAL TACHYCARDIA \*

By SYLVAN D. SOLARZ, Major, M.C., A.U.S., *Chicago, Illinois* †

THE problem of the early diagnosis of myocardial infarction in the age group of those serving in the armed forces has been difficult. In the early days of the emergency the diagnosis was not made promptly because of the lack of experience with this disease in relatively young men. The easy availability of electrocardiograms has made the diagnosis more certain in many instances, but at the other extreme there has been the tendency to err on the conservative side and to read too much into the tracings. Then too, relatively rare conditions have been called infarction without careful analysis with the resultant labelling of the patient as a "coronary case" with the unfavorable prognostic implications of that disease.

In recent years there have been several reports of instances of prolonged inversion of the T-waves in the electrocardiogram following bouts of paroxysmal tachycardia.<sup>1, 2, 3, 4</sup> The very great importance of differentiating this condition from myocardial infarction has been stressed by the writers.

Recently a 40 year old major was transferred to this general hospital from another hospital because of the deactivation of that installation. The transfer diagnosis was "recent infarct of the myocardium with nodal tachycardia secondary to the infarction, onset January 26, 1946." On arrival here an electrocardiogram was obtained (figure 1 C, March 5, 1946); it was normal. Because of the relatively short period of time that had elapsed since the onset of the disease and the finding of a normal record the patient was referred to the author for consultation. The following history was obtained.

### CASE REPORT

The patient was admitted to another Army general hospital at 8:30 a.m. January 29, 1946 complaining of a rapid heart action, inspiratory difficulty, weakness, and a "washed out" feeling of three days' duration.

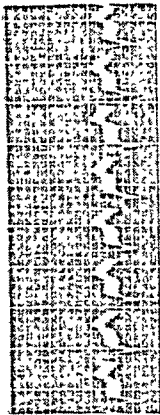
The past history was negative. The patient had always been healthy, was a hard driving, forceful type of individual and, in the Army, he had been working in a similar manner.

The family history revealed that the patient's father, aged 69, had angina pectoris. The patient's mother and son had hay-fever and asthma.

\* Received for publication November 1, 1946.

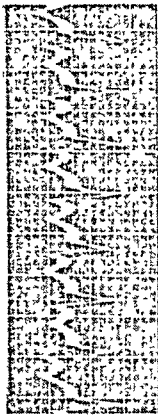
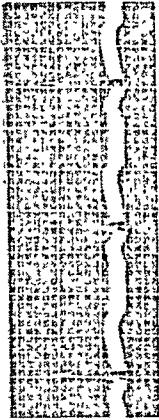
† From the Cardiovascular Section, Wakeman General Hospital, Camp Atterbury, Indiana. Present address: Michael Reese Hospital.

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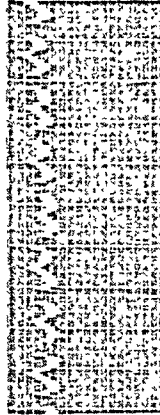
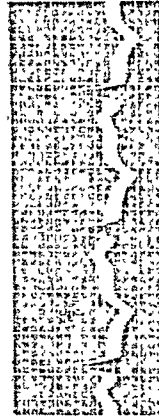


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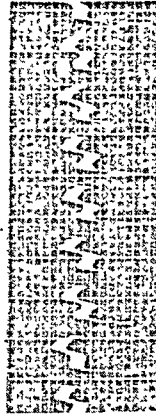
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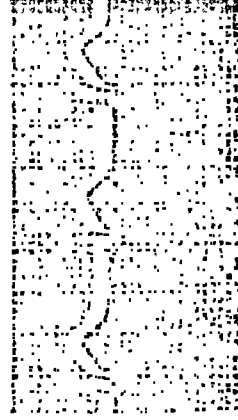
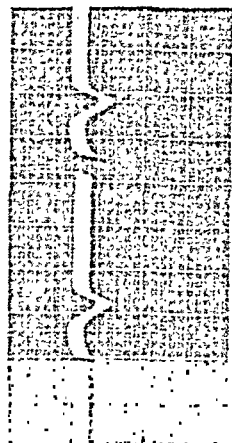
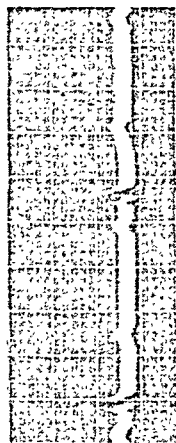
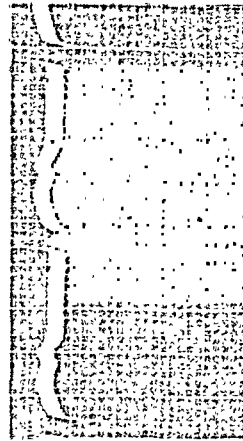
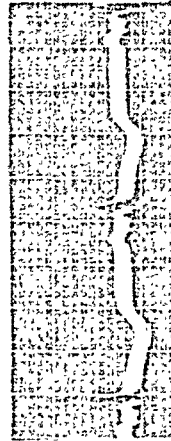
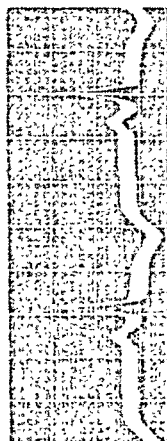


Fig. 1 A. Discussed in text. Note the characteristic bizarre T-waves especially marked in tracing on January 31, 1946.

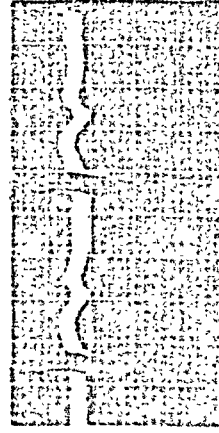
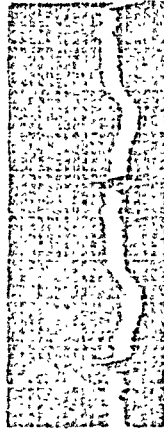
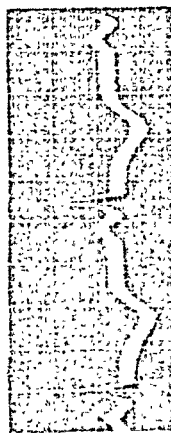
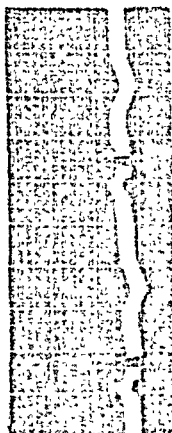
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Fig. 1 A (Continued).



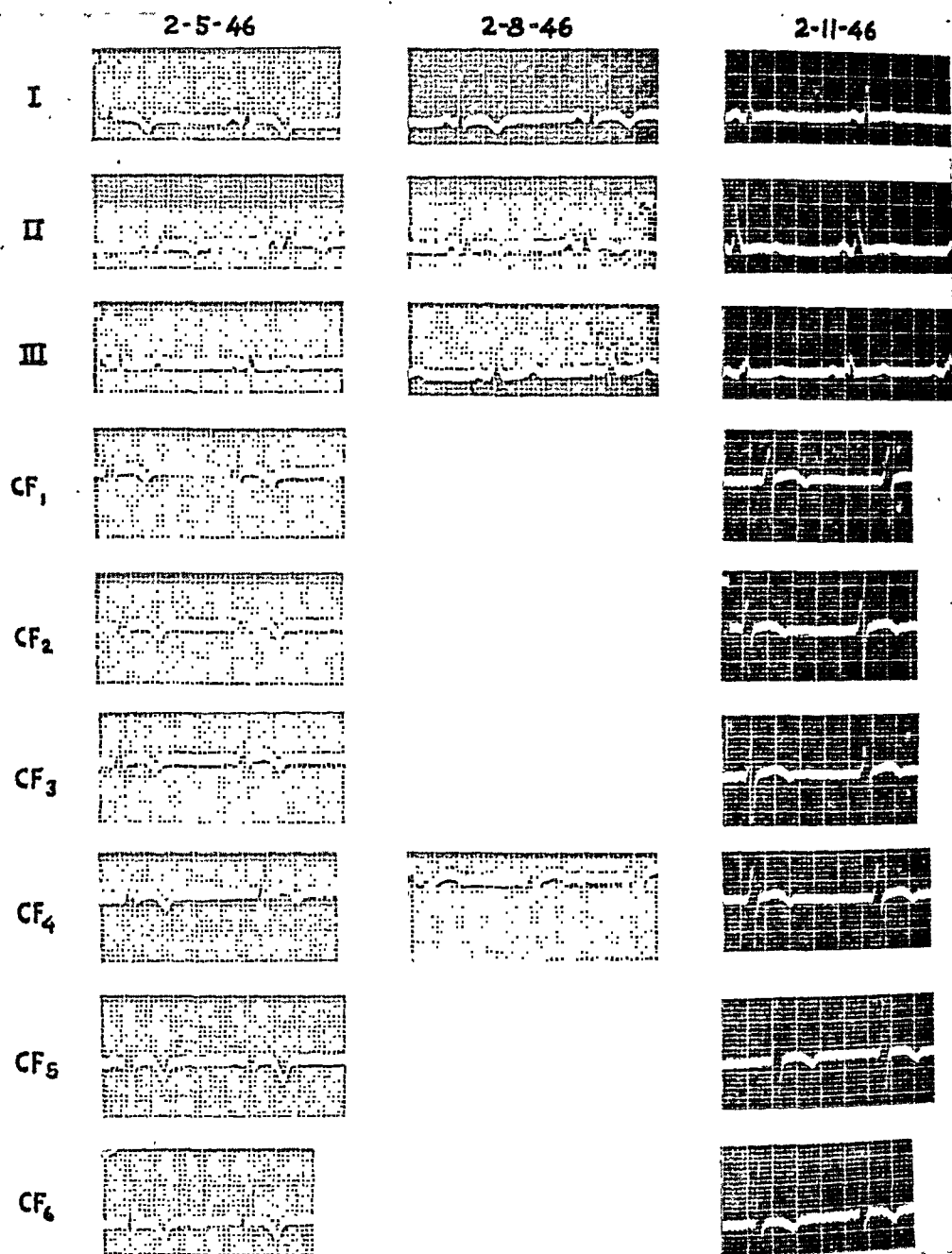


FIG. 1 B. Continuation of figure 1 A. Note the absence of QRS changes in all leads. Discussed in text.

During the week preceding the onset of his illness the patient had been flying cross country, piloting his own plane, from one post to another, working very hard and long hours. On the evening of January 26, 1946 the patient was in New Orleans. While leaving a restaurant after dinner he suddenly became aware of an extremely rapid heart beat. His gait became unsteady, his arms felt heavy, he became dizzy, and his heart "felt as if it were jumping out of his chest." On deep inspiration he

felt a knife-like pain between his shoulder blades and retrosternally. Because of the pain he was forced to limit his respiratory efforts to short, shallow respirations.

The patient was able to return to his hotel without aid. He thought he had a digestive disturbance so he induced vomiting and took an antacid without influencing the heart rate or the inspiratory pain. There was no crushing chest pain at any time. The patient was able to lie flat in bed without difficulty and eventually fell asleep. He awakened about 8:30 a.m. on January 27 and felt "washed out." There was no pain, and the patient was no longer conscious of the rapid heart rate. While eating a light breakfast he began to sweat profusely and once more became aware of the fluttering sensation in his chest. He returned to bed and felt better. After spending the day quietly in bed he was able to walk six blocks to a restaurant that night. He felt weak and was conscious of a rapid heart action, but the fluttering sensation had disappeared. After a light meal he returned to bed and slept well.

On the morning of January 28 the patient felt well enough to fly his plane a distance of approximately 500 miles in three hours. While in the air he felt normal. After landing at his destination he transacted some business for about one-half hour when he again became aware of the fluttering sensation. Nevertheless he was able to fly 500 miles farther to his home. On alighting from the plane he again became aware of the rapid heart action, inspiratory difficulty, and fluttering sensation. He became nauseated and thirsty but could not retain fluids. He went home and called his family physician who found a very rapid heart rate, administered morphine, and advised admission to an Army hospital.

On the morning of January 29 he was admitted to another general hospital. According to the clinical chart his condition was described as restless and anxious. The pulse rate was 220 a minute, the blood pressure was 70 mm. of mercury systolic and 50 diastolic, the liver edge was palpable 4 cm. below the costal margin, and the temperature was 100° F., orally. The respiratory rate was 24. An electrocardiogram was obtained (figure 1 A, 10:00 a.m., January 29, 1946) and interpreted as showing nodal tachycardia. He was immediately started on quinidine and normal sinus rhythm was present four hours later (figure 1 A, 2:00 p.m., January 29, 1946). Later that evening another paroxysm of tachycardia from a different supraventricular focus appeared (figure 1 A, January 30, 1946) but responded to increased doses of quinidine (figure 1 A, January 31, 1946).

No roentgenogram of the chest was taken. The urine was negative, the sedimentation rate was 21 mm. (Westergren, uncorrected), and the white blood count was 11,500 with 70 per cent neutrophils, 21 per cent lymphocytes, 5 per cent monocytes, and 4 per cent eosinophiles. For the first day of hospitalization the temperature was 99.4° but fell to normal thereafter. The patient was kept on quinidine until February 17 and was kept at strict bed rest with the accepted "coronary" routine.

When the patient was transferred to this hospital complete physical examination, fluoroscopy, and laboratory studies were done; all findings were entirely normal.

### DISCUSSION

On reviewing the records we were first impressed by the rapid evolution of the electrocardiographic changes. These may be noted in the illustrations (figures 1 A, 1 B, and 1 C). On February 19, just 22 days after the initial tracing the record showed only borderline T-waves in Leads I and II as the sole abnormalities (figure 1 C) and six days later the record is entirely normal.

Inspection of the second electrocardiogram taken four hours after the first (figure 1 A, 2:00 p.m., January 29, 1946) reveals normal sinus rhythm, normal QRS complexes and concordant deviation of the S-T segments and T-waves. Electrical systole, the Q-T interval, is slightly prolonged to 0.38 second with

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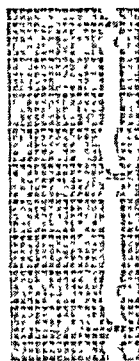
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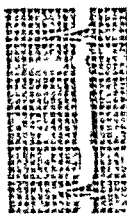
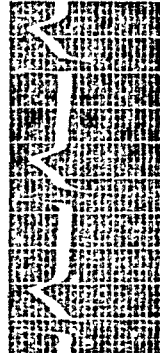
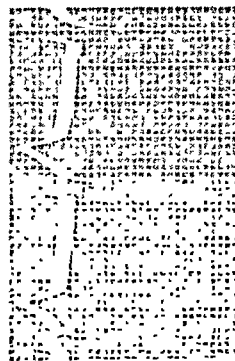
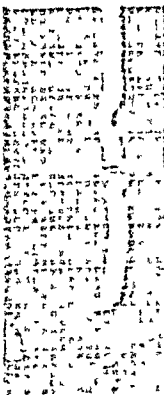
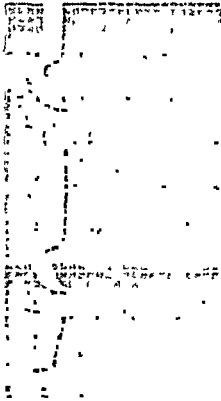
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Fig. 1 C. Continuation of previous figures. On February 25, 1946 the tracing is normal. Compare the chest leads from March 11, 1946 with those obtained on February 11, 1946 (figure 1 B). Discussed in text.

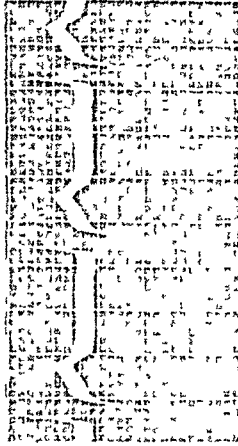
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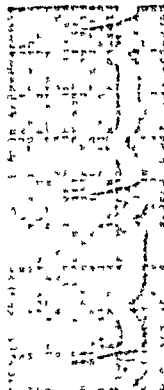
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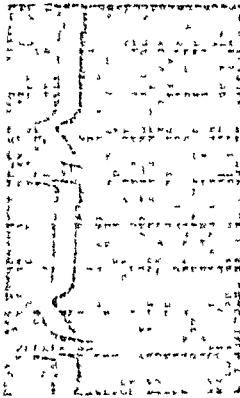
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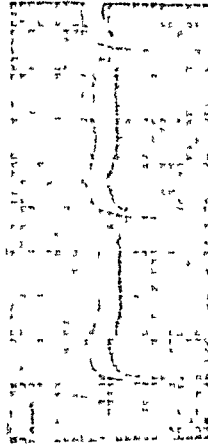
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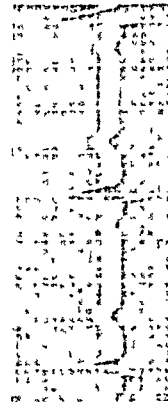
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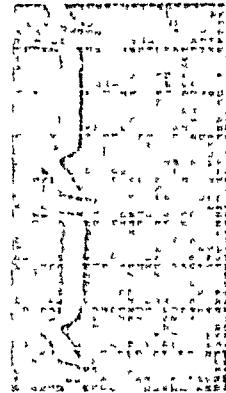
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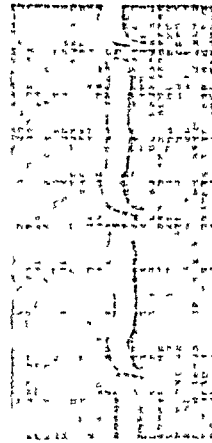


Fig. 1 C (Continued).

a normal average at this rate of 0.30 second. This prolongation is due to the widened T-wave. The T-waves are not symmetrical as would be expected in myocardial infarction.

The curve obtained on January 31, 1946 (figure 1 A) shows an electrical systole of 0.52 second while the normal averages 0.34 second. Subsequent records (figures 1 A, 1 B, and 1 C) show a steady rapid return to the normal. In the records available with six chest leads (figure 1 B) the changes are confined entirely to the inverted T-waves. None of the T-waves in the entire series of records shows any of the characteristics of the "coronary type" of T-waves, nor are there any discordant S-T and T deviations. There are no QRS changes of any significance.

A study of the illustrations published by the authors indicated previously will emphasize the points outlined as differentiating these electrocardiographic changes from those due to myocardial infarction. Ward<sup>4</sup> stresses the prolonged Q-T interval that occurs early after the cessation of the paroxysm. This is due to the bizarre, asymmetrical, and prolonged inverted T-wave in each case.

The cause of the changes is not known precisely. Campbell<sup>5</sup> believes that it is a reversible process indicating some degree of exhaustion or strain of the heart muscle. Geiger<sup>1</sup> mentions the long duration of the paroxysm in the case as a possible cause of the exhaustion. Quinidine was also mentioned as a cause, but Zimmerman's<sup>2</sup> cases showed the changes after small doses, and the present case showed the change after only 0.4 gm. of the drug.

Since paroxysmal tachycardia from supraventricular foci occurs most commonly in normal hearts the great importance of differentiating the changes described here from those due to myocardial infarction is self-evident. It is believed that such differentiation can be made readily if attention is paid to the differences described above.

#### SUMMARY

1. A case of supraventricular paroxysmal tachycardia with prolonged electrocardiographic changes is described.

2. The electrocardiographic differentiation of this condition from myocardial infarction is discussed. Following such cases of paroxysmal tachycardia there appears an inverted, asymmetrical, and prolonged T-wave of bizarre appearance. This causes a prolongation of electrical systole. Further differential points are the concordant S-T and T deviations, the asymmetrical T-waves, and the absence of QRS changes in this condition.

#### BIBLIOGRAPHY

1. GEIGER, A. J.: Electrocardiogram simulating those of coronary thrombosis after cessation of paroxysmal tachycardia, *Am. Heart Jr.*, 1943, xxvi, 556.
2. ZIMMERMAN, S. L.: Transient T-wave inversion following paroxysmal tachycardia, *Jr. Lab. and Clin. Med.*, 1944, xxix, 598.
3. EISAMAN, J. L.: Electrocardiograms simulating posterior myocardial infarction after cessation of paroxysmal tachycardia, *Am. Heart Jr.*, 1945, xxx, 401.
4. WARD, L. S.: Abnormal electrocardiogram following recovery from paroxysmal tachycardia, *Am. Heart Jr.*, 1946, xxxi, 645.
5. CAMPBELL, M.: Inversion of T-waves after long paroxysms of tachycardia, *Brit. Heart Jr.*, 1942, iv, 49.

## VOLVULUS OF THE STOMACH \*

By LEONARD CARDON, M.D., REGINA S. GREENEBAUM, M.D., and JULIAN ARENDT, M.D., *Chicago, Illinois* \*

VOLVULUS of the stomach is seldom considered in the diagnosis of acute abdominal disease. Yet it may produce symptoms as sudden and violent as the more familiar volvulus of the intestine. "Volvulus" is defined as abnormal torsion of a portion of the gastrointestinal tract sufficient to produce clinical symptoms.

The earliest reported cases of torsion of the stomach, beginning with Berti's<sup>1</sup> in 1866, were diagnosed only at autopsy. Later a number of surgeons, starting with Berg<sup>2</sup> in 1895, diagnosed the condition clinically and successfully treated it surgically. The roentgenologic appearance of torsion of the stomach has also been described.<sup>3, 4, 5, 6, 7</sup> The medical aspects and especially the clinical diagnosis have thus far received scant attention.

The rare type of acute "complete" volvulus in which the entire stomach participates, was seen in our first case. "Partial" volvulus, the rotation of part of the stomach in relation to the rest of it, was presumed to have occurred in our second patient whose stomach, even when she is asymptomatic, is peculiar in shape, size and position.

## CASE REPORTS

*Case 1.* The sudden onset of severe pain in the left upper abdominal quadrant and repeated vomiting of one hour's duration were the presenting symptoms of a 74 year old male when one of us (L. C.) saw him in consultation with his family physician, Dr. N. S. Sheffner. The pain radiated to the left costovertebral angle and the precordium. A week earlier a similar episode had occurred immediately after the patient had attempted to lift a piano. At that time a physician had made a diagnosis of acute coronary occlusion, administered morphine and advised complete bed rest. The patient remained in bed but was not entirely free from pain during the week between attacks. He had attempted to leave his bed just before the second attack. His past medical history was noteworthy only for an operation for hemorrhoids and rectal prolapse 15 years previously, and for constipation so obstinate that he had taken an enema every day for as long as he could remember.

The patient was writhing, groaning and sweating profusely because of severe pain when he was first seen. The single but strikingly abnormal finding was in the abdomen. The left upper quadrant and lower anterior chest wall were forced anteriorly by a large, palpable, firm, cystic, partially tympanitic, very tender mass.

Acute torsion of the stomach seemed the most likely explanation of this unusual clinical picture. Other diagnoses considered were acute gastric dilatation, incarcerated diaphragmatic or other internal hernia of the stomach, and acute complete pyloric obstruction perhaps superimposed on a chronic obstruction due to a stenosing ulcer or carcinoma.

Aspiration through a stomach tube seemed to be the logical treatment but without further knowledge of the nature of the obstruction it appeared hazardous to attempt it. After a roentgen-ray examination of the abdomen had revealed a high left hemi-diaphragm with a large air bubble above a fluid level in a dilated stomach, a

\* Received for publication July 5, 1946.  
From the Mt. Sinai Hospital of Chicago.

Levine tube was easily passed. A liter of thin fluid was aspirated and Wangensteen suction instituted. This considerably relieved the patient's pain. Later when drainage had stopped, the mass was still palpable and the patient, while much improved, was still uncomfortable. A large stomach tube was then inserted, a liter of thick, gruelly material aspirated and the stomach washed until the return flow was clear. This gave the patient complete relief from distress and made the tumor disappear. No bile was observed in the gastric contents at any time. The temperature, pulse rate and leukocyte count were normal.

The next day, when the patient was asymptomatic, a barium meal showed the entire stomach rotated through  $180^\circ$  so that the greater curvature was up and the lesser curvature down (figure 1 A). The organ appeared to be rolled together in the shape of a horseshoe. The cardia and pylorus were in such close proximity (figures 1 B and 1 C) that the differentiation of one from the other was difficult. The drawing, figure 1 E, based on the roentgenograms, elucidates the nature of the torsion. The pylorus was elongated and stretched. The esophageal orifice and the fundus with its air bubble were below and medial to the pylorus and duodenal bulb. A small para-esophageal hiatus hernia was found. No other gastric lesion was seen. A loop of colon was interposed between the stomach and the diaphragm. A barium enema revealed a hugely dilated, elongated and redundant colon.

Daily gastric lavage was continued. The patient was discharged on the eighth day of his illness, apparently well, with instructions to use gastric lavage if needed for a recurrence of symptoms.

Five months later another barium meal was administered. The patient had remained entirely free from symptoms in the interim. At this time the roentgen-ray showed an elongated stomach of steer horn shape (figure 1 D) in marked contrast to its previous appearance. The mucosal pattern was also normal. A loop of colon was still interposed between the stomach and the left side of the diaphragm so that the latter was pushed upward and the stomach displaced far medially.

*Case 2.* The presenting features in the case of this 35 year old woman were the sudden onset of severe upper abdominal pain and repeated vomiting. At first the vomitus contained undigested food and later only gastric juice. Still later non-productive retching occurred repeatedly. The pain was intermittent at the onset but grew progressively more severe with longer paroxysms and less complete relief between paroxysms. The patient writhed and groaned almost continuously at this time. Epigastric tenderness was marked. No rigidity was present. The temperature, pulse rate and leukocyte count remained normal during six hours of increasingly severe symptoms. Heat, cold, nitroglycerine and atropine gave no relief. An obstruction at the pylorus was considered the most likely cause of the attack because of the absence of bile in the vomitus. The pain had begun to subside spontaneously shortly before the administration of morphine and atropine seven hours after the onset of symptoms. Within 12 hours it had disappeared entirely.

Strikingly abnormal mobility of the stomach associated with peculiarity of shape and position was observed on fluoroscopy 10 days after the attack. The organ was

FIG. 1. *Case 1.* A, B and C. Torsion of stomach as it appeared 24 hours after acute attack. Stomach rotated forward and upward  $180^\circ$  about its cardio-pyloric axis. Greater curvature superior; lesser curvature inferior. Cardia below pylorus. Pylorus elongated. In A, loop of colon is interposed between stomach and left hemidiaphragm.

D. Roentgen-ray five months after A, B and C. Normal except that stomach is pushed medially by loop of colon.

E. Drawing of stomach in torsion based on roentgen-rays A, B and C.

F. Diagram. Cardio-pyloric axis of rotation, the usual axis in "complete" volvulus.

P.—Pylorus.

L. C.—Lesser curvature.

G. C.—Greater curvature.

Oes.—Esophagus.

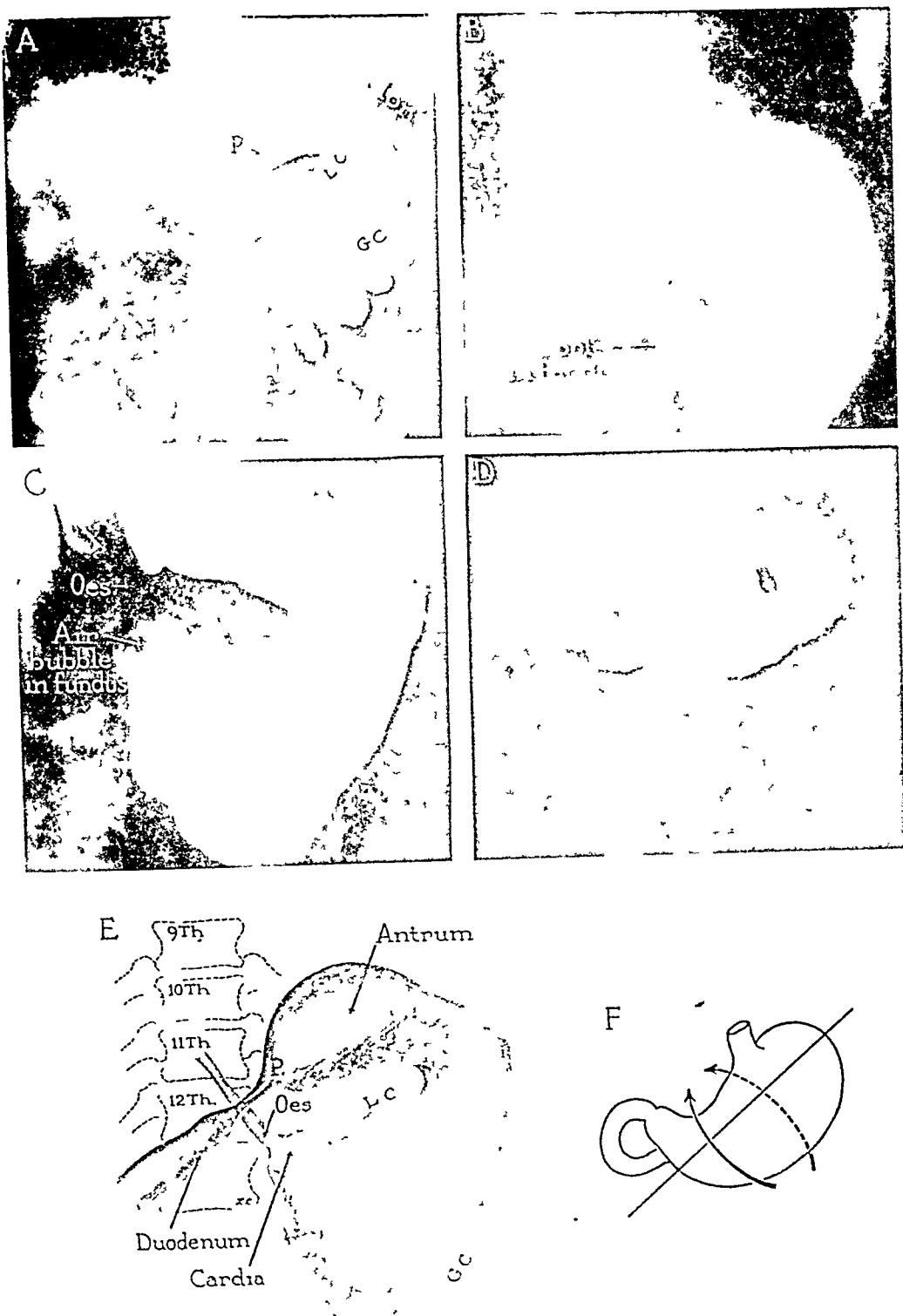


FIG 1.



divided into two portions, a hugely distended, air-containing fundus and a smaller, barium-filled corpus and antrum. The distal segment at times rotated upward so that it seemed to "ride" on the distended proximal one (figure 2 B). In this position a fold or kink seemed to be present along the line of junction with the distended fundus. A few minutes later the distal portion dropped to a more normal position (figure 2 A). These motions recurred several times in the course of the fluoroscopic examination. While abnormal movements of the stomach were so obvious to the observer, the patient had no pain. No intrinsic lesion was seen in the stomach or duodenum. Cholecystography was normal. No occult blood was found in the stool. The colon was unusually long with a triple sigmoid loop, splenic flexure high under the diaphragm, transverse colon high in the epigastrium and a redundant hepatic flexure.

Six years after the initial attack the stomach was fluoroscoped again when the patient was symptom free. It had the same shape, position and unusual mobility seen previously (figures 2 C and D) suggesting the permanence of this anatomic abnormality. In the lateral view (figure 2 E) the stomach was shaped like a partially opened jackknife with the concavity directed posteriorly and the convexity anteriorly and superiorly beneath the anterior abdominal wall. The projection of the organ in the sagittal plane occupied a much greater area than normal. The distal and more anteriorly placed chamber of the bilocular organ moved up and down about the proximal and posterior distended fundus. The ease with which a kink could be produced at the juncture of the two segments is evident.

This patient has never had a repetition of the severe pain and vomiting of the initial attack but she does get recurrent episodes of moderate epigastric pain. These usually occur after several days of fleeting, migratory abdominal pain relieved by the passage of flatus. The migratory pain is often associated with fatigue, emotional upsets, or dietary indiscretion. The epigastric pain is much more severe than the migratory pain and is invariably associated with a feeling of enough distention to make the patient wish to remove her corset. Belching never occurs. Antispasmodics sometimes bring relief. If the pain persists, the patient has found that it will disappear if she lies prone across a bed with her trunk hanging vertically, head down, at right angles to her lower extremities.

#### COMMENT

*Predisposing Conditions.* Some or all of the following underlying conditions have been found in reported cases of gastric volvulus.

*High Lying, Partially Rotated Stomach.* A stomach, partially rotated to a transverse position so that the greater curvature is anterior and the lesser curvature posterior is occasionally seen in a routine gastrointestinal examination (figure 3). This normal variant may predispose to further gastric rotation and volvulus. Such a position may also be acquired, for example, after pneumonectomy which causes displacement and rotation of the abdominal organs to fill in the empty chest cavity.

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FIG. 2. Case 2. A and B. Ten days after acute attack. Antero-posterior views taken several minutes apart. Note abnormal mobility of corpus about air-distended fundus in bilocular stomach.

L. C.—Lesser curvature.

G. C.—Greater curvature.

C and D. Six years after acute attack. Pictures taken a few minutes apart. Note similarity to A and B.

E. Lateral view, same day as C and D.

F. Diagram showing general direction of rotation in "partial" volvulus. Distal portion of stomach rotates about proximal. Axis of rotation at right angles to long axis of stomach.

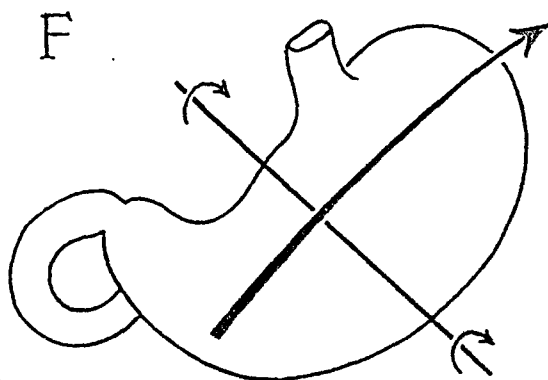
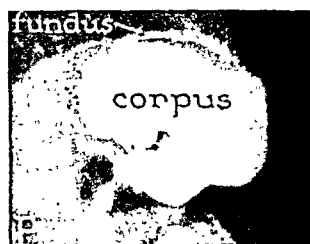


FIG. 2.

*Long Gastric Ligaments.* Surgeons have found long gastrocolic and gastrohepatic ligaments in patients with spontaneous gastric volvulus.<sup>8,9</sup> This anatomic peculiarity, congenital or associated with visceroptosis, permits excessive mobility of the stomach. Extensive gastric volvulus would be impossible without abnormally long gastric ligaments.



FIG. 3. High lying stomach partially rotated to transverse position. Greater curvature anterior. Lesser curvature posterior. A normal variant.

A. W.—Anterior wall.  
P. W.—Posterior wall.  
P.—Pylorus.

*Redundance of the colon*, mentioned in many reports, was conspicuous in our cases. Patient 1 not only had roentgen-ray evidence of redundance, but his severe and persistent constipation was a clinical manifestation of it. Several authors<sup>5,10</sup> regard gaseous distention in a redundant colon as a cause of rotation of the stomach. Schatzki and Simeone<sup>6</sup> could not produce volvulus of the stomach by experimental distention of the colon with air although the stomach was displaced upward by this procedure.

*Interposition of a loop of colon* between the stomach and the leaf of the diaphragm has been observed in patients with gastric volvulus.<sup>4,11</sup> This may be a causative or a coincidental circumstance. Gaseous distention of such an interposed colonic loop may produce the initial displacing force that leads to gastric torsion.

*Diaphragmatic Hernia.* The displacement and rotation of the stomach produced in diaphragmatic herniation or eventration is another possible cause of gastric volvulus. The small paraesophageal hiatus hernia probably played no etiological rôle in our first case.

*Vigorous peristalsis immediately after antiperistalsis* has been postulated as another means of initiating gastric volvulus.<sup>12,13</sup>

*Sudden Rise in Intra-abdominal Pressure.* The acute onset of the catastrophic symptoms in case 1 immediately after an attempt to lift a piano suggests a rise in intra-abdominal pressure as a precipitating cause of the volvulus.

*Combination of Predisposing Conditions.* The stage setting for impending volvulus of the stomach in the first case may be visualized as follows: The abdominal cavity is crowded by a dilated, redundant, over-filled colon. The entire gastrointestinal tract, including the stomach, is abnormally mobile because of congenitally long mesenteries and intra-abdominal ligaments. A loop of colon is interposed between the stomach and the left hemidiaphragm. Sudden exertion with contraction of the muscles of the abdominal wall and the diaphragm causes an abrupt diminution of intra-abdominal volume. This forces the loops and coils of the stomach and bowel to rearrange themselves within a smaller space. The stomach with its greater possible range of motion because of its abnormally long ligaments may be caught at the moment of compression in such a situation (e.g. high lying transverse position) that further rotation is easier than return to the normal position. Once it is forced beyond this critical position, the persisting pressure of the abdominal and diaphragmatic muscles acting directly on the stomach or indirectly through the interposed intestinal loops, forces it to continue its abnormal rotation to the point at which symptoms occur. After the torsion is produced, the abnormal length of the ligaments may prevent them from exerting enough tension to reduce the volvulus even after the intra-abdominal pressure is lessened. The hyperdistention of the stomach which rapidly ensues tends to hold it so tightly wedged between the surrounding organs that at operation in other similar cases it has often been found impossible to untwist or manipulate the stomach until its contents have been removed through a trocar.

Our first patient must have had suddenly increased intra-abdominal pressure many times previously in his 74 years of life, without developing gastric volvulus. When he had the acute attack either the rise in intra-abdominal pressure was greater, or the stomach was in the critical position favorable for torsion at the moment of exertion, or both may have occurred simultaneously.

*Explanation of Symptoms.* Whether or not rotation of the stomach produces symptoms depends upon the extent of disturbance in its peristaltic movements, secretion, and circulation. The tremendous gastric distention found in cases of volvulus is a consequence both of the inability of the stomach contents to escape because of the torsion and of the hypersecretion of fluid and the transudation of serum resulting from the disturbed circulation. These mechanisms explain the patients' pain as well as the enormous amount of fluid in the stomach. Maximum gastric hyperdistention in case 1 must have been far greater than the films (figures 1 B and C) show, since these were taken after more than two liters of fluid had been removed.

The repeated emesis without bile in the vomitus, followed later by non-productive retching in case 2, was probably the result of twisting of the stomach to such a degree that it became divided into two disconnected compartments. The proximal compartment remained connected with and open to the esophagus, but was separated from the distal chamber so that bile, even if it entered the stomach through the pylorus, could not pass the obstruction between the chambers and hence could not reach the esophagus. After the proximal compart-

ment had been emptied by repeated emesis, further attempts at vomiting resulted only in non-productive retching. In case 1, the degree of twisting was sufficient to explain the inability of bile to reach the esophagus.

*Types of Volvulus. Total.* When the entire stomach rotates upon itself, as in case 1, the condition is known as "total" volvulus. The stomach may twist as much as 360 degrees. In our case it must have been twisted to a greater degree at the height of the pain than the 180 degrees observed in the roentgen-ray examination 24 hours later when the patient was asymptomatic.

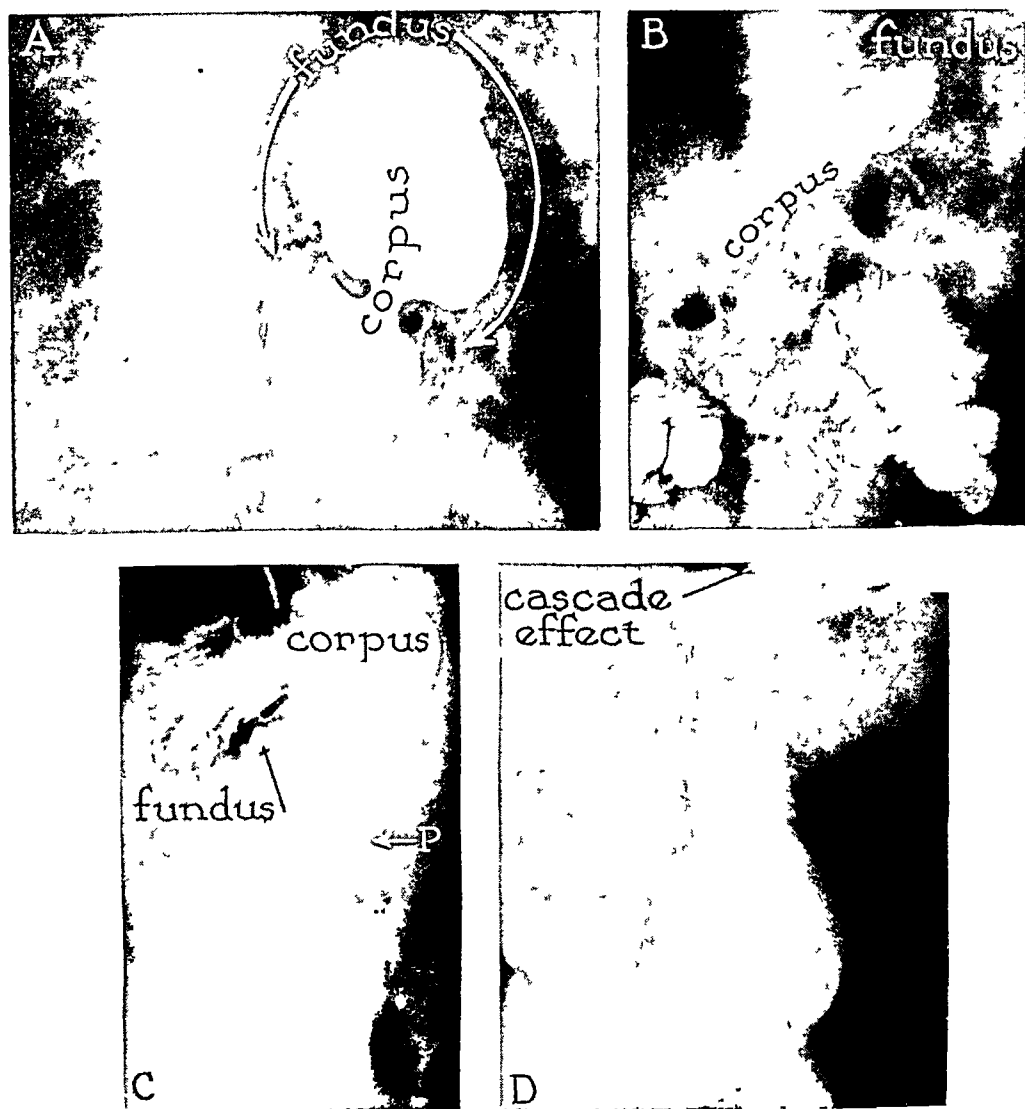


FIG. 4. Bilocular stomach of patient who complained only of left upper quadrant pain and belching of many years' duration. Not in volvulus.

A. Two chambers.

B. Small corpus extending from large, air-containing fundus, like a finger from an air-distended rubber glove.

C. Lateral view. Corpus makes sharp knee bend with fundus

P.—Pylorus.

D. "Cascade" produced by fold in redundant stomach.

The degree to which the stomach can be rotated without the production of clinical symptoms is noteworthy (figures 1 A, B and C).

*Partial* volvulus occurs when one portion of the stomach twists on another portion, as in case 2. Twisting of this type may occur if the mid-portion of the stomach is indurated or fixed by intrinsic or extrinsic lesions such as ulcer, carcinoma, hour glass stomach, adhesions or herniation through the omentum. None of these conditions was present in this case. Instead, the bilocular shape and peculiar position of the organ presumably predisposed it to abnormal rotation. The shape and position of the stomach are not unique. Figures 4 and 5 illustrate a similar gastric condition in two other patients who had no symptoms of volvulus. Their complaint was abnormal gaseous distention of the sort found in habitual aerophagia.

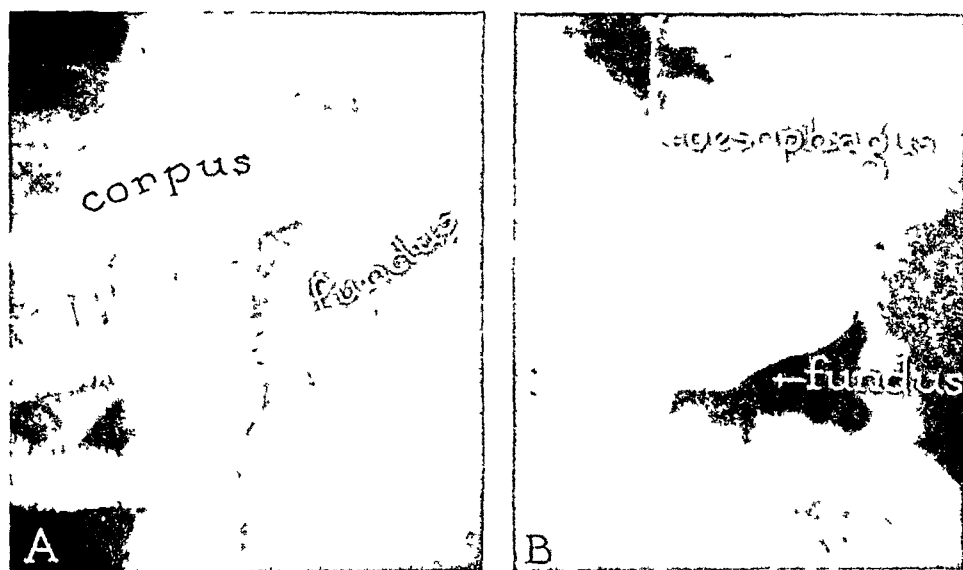


FIG. 5. Stomach similar to figures 2 and 4. Patient's only complaints were precordial pain and belching.

A. Antero-posterior  
B. Lateral.

Figure 6, the artist's conception of a lateral view of this type of stomach based on the roentgenograms in figures 2, 4 and 5, clarifies its characteristic features. The esophagus passes into a hugely distended, balloon-like fundus that lies against the posterior abdominal wall beneath the left hemidiaphragm just to the left of the spine. The entire stomach is shaped like a partially opened jackknife with its concavity posterior and to the right and its convexity just beneath the abdominal wall, anterior, superior and to the left. The upper, more or less horizontal limb of the jackknife is made up of the hyperdistended fundus from which the first portion of the corpus extends anteriorly to the abdominal wall. The corpus is much smaller than the fundus and may arise directly from it like a finger from the palm of an air-distended rubber glove (figure 4 B) or may be separated from it by a constricted portion of the stomach of some length. The lower limb of the jackknife composed of the rest of the

corpus and the pylorus, bends back more or less sharply on the upper limb at the anterior convexity or "knee." It extends posteriorly, to the right and inferiorly. The distention itself may displace the fundus downward and posteriorly to produce the jackknife shape here described. The fundus may be further depressed by a loop of colon between it and the diaphragm so that the anterior bend may actually be the most superior portion of the stomach (figure 4 C). The organ may be larger and more redundant than normal. The cascade effect in figure 4 D was produced by a fold in a redundant stomach. Abnormal mobility of the distal limb about the proximal one in an up and down, and

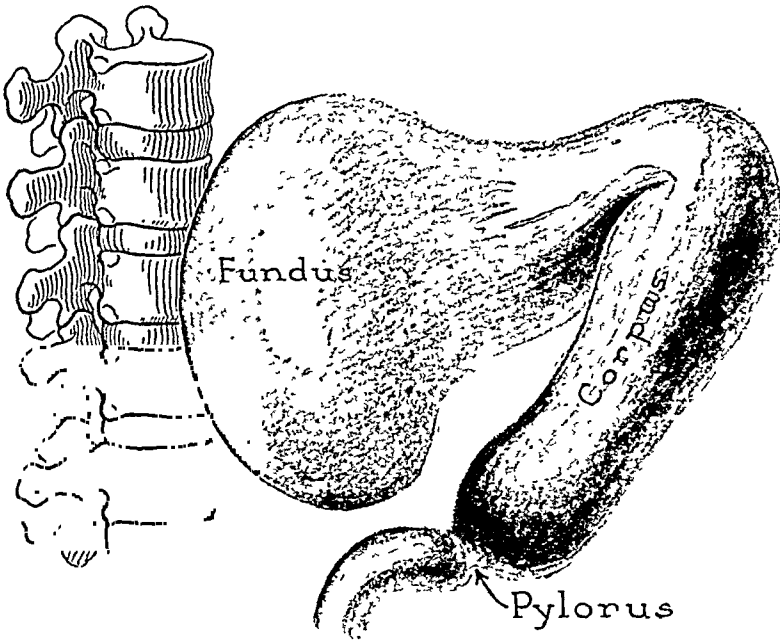


FIG. 6. Drawing of "jackknife" type of stomach based on roentgen-rays in figures 2, 4 and 5. Lateral view. Large, air-distended fundus posterior. Convexity anterior and superior. Horizontal, superior limb continuous with distended fundus.

perhaps also in a rotatory direction, was seen in these cases. To emphasize the abnormality of these stomachs, anteroposterior and lateral views of the normal organ are inserted for comparison (figure 7).

The peculiar shape and position of this type of stomach may be a congenital anatomic variation, or the hyperdistended, air-filled fundus may be a manifestation of air swallowing, although this was not observed in our patients. In infants, overdistention of the fundus is seen more often in the breast or bottle-fed, who inevitably swallow air, than in the spoon-fed.<sup>14</sup>

*Axis of Rotation.* The stomach in case 1 rotated above the cardio-pyloric axis (figure 1 F). "Complete" volvulus and severe obstruction are more likely to occur in rotations about this axis. A case with roentgenograms of a stomach similar in direction of rotation, completeness of involvement and position in volvulus was reported by Caillods and Cottet.<sup>7</sup>

The axis in case 2 was perpendicular to a line joining the cardia and pylorus (figure 2 F). This axis is more common in "partial" volvulus in which only a part of the stomach revolves about the remainder.

*Diagnosis.* The sudden onset of excruciating pain high in the abdomen, especially in its left upper quadrant, with or without a visible and palpable mass, and repeated emesis without bile in the gastric contents followed by non-productive retching, should suggest the possibility of volvulus of the stomach. A history of immediately preceding sudden increase in intra-abdominal pressure, absence of peritoneal irritation and normality of the temperature, pulse rate and leukocyte count would tend to confirm the diagnosis. In some cases where a fold is produced near the cardia by the torsion, it may be impossible to pass a stomach tube. This may be of diagnostic value.

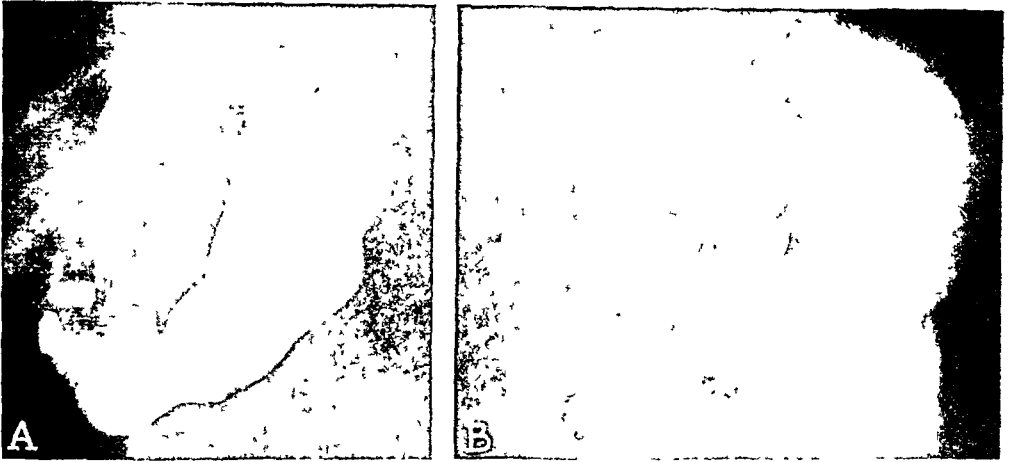


FIG. 7. Normal stomach.

A. Antero-posterior.  
B. Lateral.

Something in the clinical picture of our first case almost instinctively suggested the diagnosis. Berg<sup>2</sup> had the same feeling about his case, as indicated in the following translation from his report: "A sound was passed 47½ cm. from the teeth and here met with definite obstruction. . . . That we were dealing with a case of obstruction to the passage of food into the stomach was clear . . . and we could explain the peculiar stormy course of the illness, the stomach-like shape and location of the tumor and the obstruction to the passage of the stomach tube in no other way than by the assumption of an acute volvulus of the stomach."

The diagnosis was made in retrospect in our second case and must remain presumptive. No roentgen-ray examination was made during the acute attack. Ten days later, when abnormal mobility of a portion of the stomach was seen, no actual volvulus was present. In the absence of other gastrointestinal abnormalities and with the known unusual mobility of the distal portion of the stomach, the clinical picture of the acute attack can best be explained by assuming that the distal portion of the stomach twisted on the proximal to a sufficient degree to produce obstruction.

*Treatment. Prophylactic.* A patient who has previously had volvulus of the stomach or one whose stomach is high lying and partially rotated should avoid strain that may produce sudden, marked increase in intra-abdominal pres-



sure. Overdistention of the colon should be prevented because it might precipitate gastric torsion. A daily bowel evacuation, avoidance of gas forming foods, antispasmodics and mild sedatives may accomplish this. Large meals with their consequent overdistention of the stomach should be avoided. If gastric lavage was previously effective in the treatment of an acute attack, the patient should be taught its technic and should be urged to use it early in case of recurrence.

*Active.* The essence of the active treatment of gastric volvulus is decompression of the stomach by medical or surgical means. The first step should be an attempt at gastric aspiration and lavage. If successful, removal of the stomach contents may permit that organ to untwist itself. This is in contradistinction to a widely prevailing idea that immediate surgery is always indicated to avoid a fatal outcome. Since volvulus may produce an obstruction near the cardia, passage of a stomach tube should be performed with the greatest caution. If the stomach cannot be emptied by this method and if signs of obstruction and strangulation increase, operation is imperative.

In patients with partial volvulus, antispasmodics may stop mild attacks, perhaps by reduction of the strong peristalsis that may produce a kink between the portions of a bilocular "jackknife" stomach. If an attack persists, the patient should assume a position in which the trunk hangs vertically, head down. This maneuver is advised on an empirical basis because of its benefit to our second patient.

#### SUMMARY

Two cases of volvulus of the stomach with recovery without surgery are reported.

Acute "complete" gastric volvulus occurred in the first case. The probable underlying anatomic peculiarities associated with this condition are: a high-lying, partially rotated stomach, long gastric ligaments, redundancy of the colon and interposition of a loop of colon between the stomach and the left hemidiaphragm.

The significance of a marked increase in intra-abdominal pressure following sudden effort is stressed as a precipitating factor in this disease.

Acute "partial" gastric volvulus presumably occurred in the second patient whose stomach has a characteristic anatomic variation in shape and position which we have named "jackknife" stomach.

The outstanding diagnostic features of our cases were: severe pain high in the epigastrium or left upper abdominal quadrant, repeated vomiting without bile in the vomitus (followed by non-productive retching in our second case) and absence of evidence of inflammation. The combination of these phenomena with a history of sudden, marked, straining effort, and the rapid appearance of a left upper quadrant mass, tender and cystic, pushing the left costal arch anteriorly, suggested the clinical diagnosis in our first case.

A stomach in volvulus, even with severe symptoms, may spontaneously untwist itself.

The essence of the active treatment of gastric volvulus is decompression of the stomach by medical or surgical means.

## BIBLIOGRAPHY

1. BERTI, A.: Singolare attortigliamento dell' esofago col duodeno seguito da rapida morte, *Gazz. Med. Ital. Prov. Venete*, 1866, ix, 139.
2. BERG, J.: Zwei Fälle von Axendrehung des Magens; Operation; Heilung, *Nord. Med. Ark.*, 1897, n.f. viii, Festbd. of Axel Key no. 19, 1.
3. ROSSELET, D.: Contribution à l'étude de volvulus de l'estomac, *J. de Radiol. et d'Electrol.*, 1920, iv, 341.
4. SINGLETON, A. C.: Chronic gastric volvulus, *Radiology*, 1940, xxxiv, 53.
5. CHOISY, R., and BABAIANTZ, L.: Contribution à l'étude de volvulus de l'estomac, *Acta Radiol.*, 1927, viii, 410.
6. SCHATZKI, R., and SIMEONE, F. A.: Volvulus of the stomach, *Am. Jr. Digest. Dis.*, 1940, vii, 213.
7. CAILLODS, G., and COTTET, P.: Volvulus sub-total et volvulus total de l'estomac, *Jr. de Radiol. et d'Electrol.*, 1929, xiii, 497.
8. GABOR, M. E.: Volvulus of the stomach, *Am. Jr. Surg.*, 1940, I, 104.
9. MORRISON, W. A.: Torsion and volvulus of the stomach, *Surg., Obst. and Gynec.*, 1931, lii, 871.
10. LEBON, J., LOUBEYRE, J., and BLONDEAU, A.: Volvulus intermittent de l'estomac chez un malade atteint de dolichocolon, *Arch. d. mal. de l'app. digestif*, 1933, xxiii, 413.
11. JUTRAS, A., and TETRAULT, E.: Éventration diaphragmatique droite avec volvulus organo-axial sous-bulbaire de l'estomac et interposition hépato-diaphragmatique de l'angle droit du colon, *Union méd. du Canada*, 1937, lxvi, 49.
12. KOCHER, T.: Ein Fall von Magenvolvulus, *Deutsch. Ztschr. f. Chir.*, 1914, cxxvii, 591.
13. BUCHANAN, J.: Volvulus of the stomach, *British Jr. Surg.*, 1930, xviii, 99.
14. SCHINZ, H. R., BAENSCH, W., and FRIEDL, E.: *Lehrbuch der Röntgendiagnostik*, 1932, Georg Thieme, Leipzig, ii, 445.

## PERITONITIS COMPLICATING A CASE OF NEPHROSIS: TREATMENT WITH PENICILLIN INTRAPERITONEALLY \*

By LOUIS LEVY II, M.D., *New Orleans, Louisiana*

### CASE REPORT

J. G., white male, aged 12 years, was admitted on December 10, 1944 with a chief complaint of generalized swelling. Nine days previously the patient had developed a "cold" which continued for one week and was accompanied by a low grade fever and general malaise. The patient then noticed a progressive swelling beginning first in the eyelids, and later involving the ankles, legs, hands, and abdomen. The rest of his history was noncontributory.

Physical examination on admission revealed temperature of 99° F., respirations 30, pulse 120, and blood pressure 120 mm. of mercury systolic and 70 mm. diastolic. The only pertinent point on physical examination was anasarca, with four plus pitting edema of the lower extremity, ascites, and marked facial edema. Ophthalmoscopic, cardiac, and pulmonary examinations revealed no abnormalities.

Laboratory examinations on this admission revealed the following: Daily urinalyses showed specific gravity varying from 1.009 to 1.024, 3 to 4 plus albumin, and occa-

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From the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana at New Orleans.

sional hyaline and fine granular casts. Red blood cells were never found. Repeated blood counts revealed red blood cells varying from 4.5 to 4.9 million; hemoglobin varying from 12.5 gm. to 15.5 gm.; white blood cells varying from 12,500 to 15,950, with 74 to 79 per cent polynuclears, 1 to 4 per cent eosinophiles, 2 to 5 per cent monocytes, and 15 to 20 per cent lymphocytes. Urea nitrogen varied from 10 to 13.1 mg. per cent, cholesterol from 454 to 555 mg. per cent, serum protein from 4.5 to 5.79 gm. per cent (A/G ratio of 1 to 1). Blood Kline and Kolmer tests were negative. The phenolsulphonaphthalein test showed 70 per cent excreted in the first hour and 15 per cent in the second hour. A roentgenogram of the chest was reported as showing a normal configuration of the cardiac shadow. Intravenous pyelograms showed the kidney shadows to be normal in size, shape, and position. Pelvis, calices, ureters, and bladder appeared to fill in a normal manner. An electrocardiogram was within normal limits. Complete dental roentgen-rays were negative.

On the basis of a negative past history for kidney disease, absence of hypertension, presence of anasarca, repeated findings of four plus albumin on urinalysis without red cells, evidence of good renal function, lowered serum protein with lowered A/G ratio, the patient was considered to be either a case of nephrosis or the nephrotic stage of glomerulonephritis. The treatment consisted of repeated blood and plasma transfusions, amino acids given orally and intravenously, low salt diet, and the use of diuretics. Edema decreased somewhat, and the general condition remained good. He was discharged to the out-patient clinic on February 16, 1945.

The patient was readmitted on March 24, 1945 because of increasing edema. The findings on this admission revealed no essential changes from those found on the previous admission with the exception of an increase in the degree of anasarca. The blood pressure was 118 mm. of mercury systolic and 65 mm. diastolic. Urinalysis showed the same findings as previously except that in one specimen eight red blood cells per high power field were found. The blood count remained the same. Urea N remained below 16 mg. per cent. Serum proteins varied between 3 and 4.5 gm. per cent, and the A/G ratio was 1/1.7. The phenolsulphonaphthalein test showed 50 per cent excreted in the first hour and 15 per cent in the second hour.

On treatment similar to that given on the previous admission, the patient remained afebrile, and improved. On April 29, 1945 his temperature rose to 104° F., and he developed severe generalized abdominal pains accompanied by nausea and vomiting. There was no diarrhea. An increase in the degree of abdominal distention was noted with a tympanitic note on percussion around the umbilical region. There was exquisite generalized abdominal tenderness and rebound tenderness. Physical examination of the chest and a roentgenogram were negative at this time. Urinalysis was the same as previously. The patient developed the typical picture of an acute severe generalized peritonitis. A diagnosis of peritonitis complicating nephrosis was made and a paracentesis was performed yielding 4000 c.c. of white turbid fluid which showed gram positive diplococci on smear. A diagnosis of a pneumococcal peritonitis was considered most probable and 100,000 units of penicillin in 100 c.c. of normal saline were injected into the abdominal cavity along with the continuous use of 20,000 units of penicillin intramuscularly every two hours. On the next day, following removal of 500 c.c. of turbid fluid, 100,000 units of penicillin in 200 c.c. of normal saline were introduced into the peritoneal cavity. The patient's general condition showed a marked improvement, his temperature dropped to 100° F., and his abdominal symptoms were diminished in severity. During the next three days repeated paracenteses were performed with instillation of 40,000 units intraperitoneally each time. Repeated cultures of the fluid were negative. The peritoneal fluid became less turbid, the patient's abdominal symptoms completely disappeared, and he became afebrile. Repeated blood cultures, blood agglutinations, stool cultures and examinations were negative during and following this febrile period.

Following this episode the patient's anasarca began to subside. He received the same treatment given on his first admission and was given 100 gm. of Essenaminate\* daily by mouth. His weight dropped from 94 lbs. to 79 lbs., and most of his edema subsided. Urinary abnormalities disappeared except for a trace of albumin. Repeated quantitative urinary albumin determinations performed prior to his peritonitis had shown as much as 121.8 gm. of moist albumin in 24 hrs. After his attack of peritonitis subsided the excretion fell to 4 gm. in 24 hrs.

On June 23, 1945 he was discharged to the out-patient clinic. At that time his weight was 87 lbs., and his urine showed a trace of albumin. He has been followed in the clinic over the past seven and a half months, and although his general condition has remained the same and his weight has only increased to 98 lbs., his urinary albumin has again become four plus, and his serum proteins are 3.37 gm. per cent with an A/G ratio of 1/1.2. Blood urea N has remained below 10 mg. per cent, and the phenolsulphonephthalein excretion has varied between 65 and 75 per cent.

#### COMMENT

A case of lipoid nephrosis (or the nephrotic stage of glomerulonephritis) complicated by pneumococcal peritonitis is presented. The peritonitis cleared rapidly under therapy with penicillin intraperitoneally and intramuscularly.

We realize that spontaneous recovery from pneumococcal peritonitis in cases of nephrosis is not uncommon. The severity of this patient's symptomatology with the early response to therapy leads us to believe that the course of his illness was definitely beneficially altered by administration of penicillin.

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### HEMOLYTIC ANEMIA COMPLICATING PRIMARY ATYPICAL PNEUMONIA WITH COLD ISOHEMAGGLUTININS†

By BIAGIO BATTAGLIA, *Brooklyn, N. Y.*

HEMOLYTIC anemia of varying severity, associated with cold isohemagglutinins, in primary atypical pneumonia has been previously reported.<sup>1, 2, 3</sup> In a series of 200 cases, hemolytic anemia was noted in 11.<sup>2</sup> It occurred at a time when the maximal titer of cold agglutinins is most often encountered, between the middle of the second and the middle of the fourth week. The presence of cold agglutinins in high titer does not necessarily result in such hemolytic phenomena.<sup>3</sup> In some of the previously reported cases the administration of a sulfonamide compound has been considered a contributory cause of the hemolytic crisis.<sup>1</sup>

The following case history is being reported because a severe hemolytic crisis, associated with a high titer and high thermal activity of cold agglutinins, occurred during an episode of primary atypical pneumonia. Cold isohemagglutinins were still demonstrable in the patient's blood in high titer two months following the acute hemolytic crisis. No sulfonamide compound was administered during her illness. A transfusion of blood was complicated by the presence of Rh antibodies.

\* A hydrolysate of lactalbumin, supplied us by Frederick Stearns & Co.

† Received for publication March 6, 1947.

## CASE REPORT

Mrs. N. G., a 68 year old mother of five children, was admitted to the hospital on December 13, 1946. The patient was a known diabetic under my private care since 1937. Two weeks prior to admission, she developed an unproductive cough. One week later, physical examination revealed signs of a severe bronchitis throughout the chest. She was afebrile and her color appeared to be good. A mixture of codeine, ephedrine and Stokes expectorant, in addition to 10 drops t.i.d. of a saturated solution of potassium iodide, was prescribed. The next day, the patient and her family noted for the first time that her urine was dark red. This discoloration persisted for a few days. The cough became more severe. The patient was reexamined three days prior to her admission to the hospital. At that time, she appeared unusually pale; wheezy respiratory sounds were most pronounced over the right upper lobe; the rectal temperature was 100.5°. A urine specimen appeared orange in color but was otherwise not remarkable. Penicillin solution intramuscularly was administered every three hours for three days prior to hospitalization.

On admission to the hospital, the patient appeared paler, weaker and more dyspneic than she had previously been. She coughed continuously and raised very little sputum. Her temperature was 99, pulse 90, blood pressure 170 mm. Hg systolic and 80 mm. diastolic. Sibilant râles were audible in the right upper lobe and, to a less extent, in the remaining lung fields. The heart sounds were normal. The abdomen was slightly distended. The liver and spleen were not palpable. Rectal examination revealed dark brown feces. A roentgenogram of the chest revealed normal lung fields. Penicillin therapy was continued and elixir terpene hydrate with codeine was substituted for her previous cough medications.

Laboratory examinations of the blood on the morning following admission to the hospital revealed: 6.9 gm. or 43 per cent hemoglobin; 29,000 white blood cells with a differential of 52 per cent polymorphonuclears, 38 per cent lymphocytes, .9 per cent monocytes, 1 per cent eosinophiles, and 32 nucleated red blood cells per 100 white blood cells. The red blood cells were polychromatophilic and varied in size and shape; a red blood cell count was not done because the blood clotted in the pipette immediately after it was drawn. For the same reason a number of smears had to be pulled before a satisfactory one was obtained. The urine examination revealed a specific gravity of 1.020, no albumin, 1 plus sugar, no acetone and an occasional white blood cell.

Following the report of these laboratory findings, it became apparent that the patient was suffering from a hemolytic crisis associated with cold isohemagglutinins. The next day, December 15, 1946, her condition appeared worse. The blood hemoglobin was reported as 5.7 gm. Reticulocytes in a blood smear were 15 per cent of the red blood cells. The patient's blood group was O. A urine examination revealed the presence of urobilinogen to a dilution of 1:50, a negative benzidine test for occult blood, and the absence of bile. That evening, blood was withdrawn for the estimation of the cold agglutinin titer, blood fragility, icterus index, and Rh grouping. A warm syringe was used to prevent immediate clotting of the blood. One thousand c.c. of Rh positive whole blood from a blood bank was cross matched with the patient's blood, and then slowly transfused into the patient. Precautions were taken to keep the blood warm. No untoward reaction occurred during the transfusion. The next morning the patient appeared to be definitely improved.

The laboratory reported cold agglutinins to be present to a dilution of 1:2048 at icebox and room temperatures, and absent at incubator temperatures. Determination of the fragility of the red blood cells revealed beginning hemolysis at a NaCl concentration of .48 per cent, and complete hemolysis at .36 per cent. The icterus index was 20.7 units, and bilirubin determination .55 mg. per cent at 15 minutes. The patient's blood was Rh-negative.

On the afternoon of following day, December 16, 1946, the patient's temperature rose for the first time from 100 to 102° F. It remained elevated for another 24 hours, then began to fall by lysis and remained below 100° from December 19 until she was discharged to her home on December 29. During the height of her febrile reaction, she developed clinical jaundice for a few days; the physical signs in the chest increased; slight cyanosis appeared and required nasal oxygen; penicillin was discontinued and streptomycin was administered in a dosage of 1600 mg. daily from December 17 to December 21. After the acute febrile reaction subsided, her general condition improved. On the day she was discharged from the hospital, she was still very pale; physical signs were still present in the chest.

In addition to the treatment noted, she received 15 units of a concentrated liver extract intramuscularly daily, ferrous sulfate and multiple vitamin capsules. The diabetes was controlled with insulin.

Laboratory examination following the transfusion of blood revealed: on December 16, 8 gm. or 53 per cent hemoglobin, 13,300 white blood cells, with a differential of 63 per cent polymorphonuclear cells, 23 per cent lymphocytes, 6 per cent monocytes, 6 per cent eosinophiles, 2 per cent basophiles; on December 18, 7.2 gm. or 46 per cent hemoglobin; and on December 26, 47 per cent hemoglobin and 2,200,000 red blood cells. Urine examinations were performed daily for three days following the transfusion. A benzidine test for occult blood was consistently negative. The presence of bile in the urine was reported for the first time on December 19.

Following the patient's discharge to her home, 10 mg. daily of folic acid was substituted for the liver extract. On February 17, 1947, she appeared to be in excellent health. The lungs were clear. Fluoroscopic examination of the chest was negative. Her blood hemoglobin was 14 gm. (Sahli), and a blood smear was normal. A blood cold isohemagglutinin determination was positive to a dilution of 1:512 at 5° C., and negative at a room temperature of 20° C.

An Rh factor determination of her husband's blood was reported as positive. A review of the patient's past pregnancies revealed that she had given birth to seven living children. The second and fourth children both died when 22 days old of "blood poisoning." She spontaneously aborted a two months pregnancy, two years before her youngest living child, aged 23 years, was born. She had never received a transfusion of blood prior to her recent illness.

### SUMMARY

1. A case of hemolytic anemia complicating primary atypical pneumonia, associated with cold isohemagglutinins of high titer and high thermal activity is reported.

2. The cold isohemagglutinins were still demonstrable in the patient's blood two months after the acute hemolytic crisis. They were present in a dilution of 1:515 at 5° C., though absent at temperature of 20° C., at this time.

### BIBLIOGRAPHY

1. DAMESHEK, W.: Cold hemagglutinins in acute hemolytic reactions, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 77-80.
2. FINLAND, MAXWELL, et al.: Cold isohemagglutinins in primary atypical pneumonia, *Jr. Clin. Invest.*, 1945, xxiv, 458-473.
3. YOUNG, L. E.: Clinical significance of cold hemagglutinins, *Am. Jr. Med. Sci.*, 1946, ccxi, 23-39.

## EDITORIAL

### NOTES ON THE PROBLEM OF BLEEDING PEPTIC ULCER

THOUGH it is not possible to determine the mortality rate from hemorrhage in peptic ulcer, available statistics are sufficient to prove that the condition is frequently fatal. Moreover there is no evidence that the percentage of fatalities has decreased in the last two decades.

There are a number of difficulties in arriving at a dependable mortality rate from the literature. The standards for *diagnosis* of peptic ulcer vary in different series reported. Practically all series deal only with patients admitted to hospital, thus omitting many instances of minor hemorrhage treated in the home, and no doubt a few of sudden death outside the hospital due to fulminating hemorrhage. Certain papers deal only with cases of severe or massive hemorrhage. In many reports hemorrhage from peptic ulcer is dealt with merely as a subdivision of the general subject of hematemesis, thus omitting those cases in which melena is the only manifestation of the bleeding. Certain series are compiled exclusively from cases which have been treated by one type of regime, those admitted in a terminal state not being included. Some authors draw distinctions between the death rate due to the hemorrhage alone and that due to such complications as perforation or myocardial damage. It is not surprising then that reported mortality rates vary from zero to 50 per cent, with the larger and more inclusive groups usually showing 4 to 10 per cent fatalities.

Such variations in criteria, together with the relatively small number of cases in many reported series, probably account in larger measure for the incongruity of published statistics on the mortality of bleeding ulcer than do the variations in the methods of treatment in the reporting institutions. This point of view is supported by consideration of the many factors which may influence survival or death in bleeding from the ulcerations of the stomach and duodenum which are grouped clinically as peptic ulcers. Certain of these factors are not only variable in occurrence but also little influenced by dietetic regimes or modes of supportive therapy.

Though the literature contains relatively few analyses of the causes of death in bleeding peptic ulcer enough data are available to indicate that these are divisible into three classes: (1) the rapidity and volume of the hemorrhage; (2) complications occurring coincidentally with or as a consequence of the hemorrhage; (3) the presence of other disease conditions in the patient which play a part in determining the outcome.

There is no question but what loss of blood is the cause of death in the majority of fatalities associated with the condition under discussion; though it by no means accounts for all deaths. Various authors have studied separately the cases showing evidence of massive hemorrhage and all concur in

the higher mortality in this group. In Heuer's <sup>1</sup> clinic 161 cases were classified as severe or massive hemorrhage from peptic ulcer and in this group a mortality of 13 per cent occurred. Bohrer <sup>2</sup> collected, from hospital statistics and from a questionnaire to leading surgeons, data on 1556 cases of massive hemorrhage showing a mortality rate of 17 per cent. Chiesman,<sup>3</sup> in reviewing 191 cases of severe hemorrhage from peptic ulcer, found that 25 per cent had died. Bennett and his associates <sup>4</sup> in a series of 122 cases in which the alterations in total blood volume were followed during hemorrhage, found that the deaths that occurred were confined to the group showing the most severe diminution in blood volume. Similar data indicating the major rôle of blood loss in causing fatalities have been published by Allen and Benedict,<sup>5</sup> Rafsky and Weingarten <sup>6</sup> and others.

While it is not difficult in retrospective analysis to demonstrate that severe hemorrhage carries statistically a greater risk of death than moderate bleeding, it is difficult to draw valuable therapeutic deductions from this knowledge at the bedside. The clinical course of bleeding in such patients is extremely varied. Occasionally bleeding from peptic ulcer is fulminant from the onset and the patient dies in collapse within a few hours.<sup>7</sup> On the other hand the initial bleeding may be mild but a rapidly fatal recurrence may appear several days later. Quite rarely there is an apparently continuous slow bleeding with death after a week or more. The type however, most commonly seen in fatal cases consists of recurrent severe hemorrhages over a period of a number of days, each signalized by vomiting of blood and often by simultaneous passage of bloody stools, accompanied by profound drop in blood pressure, dyspnea, restlessness, apprehension and other evidences of shock.

Acquaintanceship with these various types of fatal bleeding does not assist greatly in predicting a fatal outcome in the individual case, for entirely similar clinical symptoms and laboratory evidences of severe blood loss are seen in cases which, though obviously in great danger, yet stop bleeding and recover. In fact statistics of massive hemorrhage indicate that at least four out of five recover.

It is true that abundant statistical evidence exists that death as a result of loss of blood in these cases of peptic ulcer is far more apt to occur in patients over 40 years of age than in the younger age group but since it does

<sup>1</sup> HEUER, G. J.: The treatment of peptic ulcer, 1944, J. B. Lippincott Co., Philadelphia.

<sup>2</sup> BOHRER, J. V.: Massive gastric hemorrhage, *Ann. Surg.*, 1941, cxiv, 510.

<sup>3</sup> CHIESMAN, W. E.: Mortality of severe hemorrhage from peptic ulcer, *Lancet*, 1932, cxiii, 722.

<sup>4</sup> BENNETT, T. I., DOW, J., See SANDERS, F. P., and WRIGHT, S.: Severe hemorrhage from the stomach and duodenum, *Lancet*, 1938, ii, 651.

<sup>5</sup> ALLEN, A. W., and BENEDICT, E. B.: Acute massive hemorrhage from duodenal ulcer, *Ann. Surg.*, 1933, xcvi, 736.

<sup>6</sup> RAFSKY, H. A., and WEINGARTEN, M.: Bleeding peptic ulcer, *Jr. Am. Med. Assoc.*, 1942, cxviii, 5.

<sup>7</sup> HINTON, J. W.: Fatal hemorrhage in peptic ulcer treated conservatively, *Am. Jr. Surg.*, 1933, xxii, 315.



occur at any age, there is no security to be felt in the case of a younger individual.<sup>2, 6, 8, 9</sup>

The postmortem examination of cases of peptic ulcer that have died of hemorrhage usually shows a chronic ulcer of the lesser curvature of the stomach or of the posterior wall of the duodenum with, in its fibrous base, a wide open artery. However, the ulcer may be acute rather than chronic or be a mere erosion difficult to detect without careful search. The pathological lesions in the cases of massive hemorrhage which recover spontaneously are less well known. Later roentgenological studies after recovery may indicate the site of the ulcer, but in a considerable percentage of cases yield entirely negative findings.

The importance in therapeutic management of combating the effects on the patient of excessive blood loss is generally acknowledged. Earlier regimes of starvation and markedly restricted diet were aimed at providing a period of immobility of the upper digestive tract in the hope of promoting closure of the bleeding vessel. A more generous intake of food is now employed by most physicians in the hope of supporting the patient's strength during the bleeding period. No evidence has been produced that moderately high caloric intakes of bland foods aggravate the bleeding. On the other hand the expectations aroused in some that Meulengracht's<sup>10</sup> heavy and coarse diet would radically lower the death rate have not been fulfilled. Consideration of the pathology of fatal cases makes it evident that diet alone could not be expected to stop the arterial bleeding.

The former fear of replacing the loss in blood volume by transfusion of whole blood and plasma and by a more liberal fluid intake has largely disappeared. There is no doubt in the minds of those who have used these supportive measures freely that they are frequently life saving. Bennett and his associates<sup>11</sup> have made a valuable contribution to our knowledge of the indications for transfusion by following the levels of total plasma and total cell volumes in cases of recurrent bleeding from peptic ulcer.

The difficulty in predicting the outcome in the individual case either on the basis of clinical character of the bleeding, laboratory evidences of its extent, age of the patient, or knowledge of the site of the lesion is naturally a deterrent to early operative treatment. A further deterrent is the fact that surgical opinion generally favors resection as the operation of choice, a procedure which at best involves of itself a mortality rate of approximately 5 per cent. Unless performed early before the patient's condition has deteriorated, that is when the prognosis for spontaneous cure seems brightest, the mortality rate is prohibitive. On the average the percentage of fatalities after resection in massive hemorrhage is about the same as that shown by

<sup>8</sup> BULMER, E.: The mortality from haematemesis, *Lancet*, 1927, cxiii, 168.

<sup>9</sup> BULMER, E.: Mortality from haematemesis, *Lancet*, 1932, cxxiii, 720.

<sup>10</sup> MEULENGRACHT, E.: The medical treatment of peptic ulcer and its complications, *Brit. Med. Jr.*, 1939, ii, 321.

<sup>11</sup> BENNETT, J. I., DOW, J., and WRIGHT, S.: Severe hemorrhage from stomach and duodenum, *Lancet*, 1942, cxliii, 550.

conservative treatment. The surgeon, however, deals with cases selected for severity.

It must be recalled also that upon exploring the abdomen the surgeon will not infrequently be unable by inspection or palpation to locate the point of bleeding. In this case he will be forced to choose between closing without accomplishment or performing a radical resection hoping to include the source of hemorrhage.<sup>12</sup> This situation is seldom discussed in recent surgical literature.

A conservative position at the present time is to restrict operation to patients in the older age groups; in whom available evidence indicates the presence of a chronic gastric or duodenal ulcer; who have bled dangerously once but not repeatedly; and have rallied before going on the table.

It is evident, however, that the decision for or against surgery in the individual case is a very difficult one and that the physician requires better methods than are now available for estimating in each instance the relative risks under conservative or surgical treatment.

In the face of the emergency created by active hemorrhage there is a tendency to underestimate the part played in the death rate of bleeding peptic ulcer by complications. Perforation occurring coincidentally with hemorrhage is not uncommon and in the presence of shock may be readily overlooked. In Bulmer's<sup>8,9</sup> 38 fatal cases of bleeding peptic ulcer in which postmortem examinations were made there were two instances of perforation. In Goldman's<sup>13</sup> 56 deaths, perforation had occurred in six. While the incidence reported by these two authors is unusually high, the possibility of perforation should be considered in all cases irrespective of age or extent of the hemorrhage. A further complication of hemorrhage especially in older people is the occurrence of cardiac damage evidenced by abnormal rhythms, frank congestive failure or cardiac infarction.<sup>14</sup> Cerebral thrombosis is not infrequently listed as a contributory cause of death. The lowered resistance of these patients may be held accountable for the frequent occurrence of lobar and bronchopneumonia. Parotitis is occasionally observed.

There is a known relationship between ulcer of the duodenum and chronic nephritis with uremia. Reports of gastroduodenal ulceration in association with hepatic cirrhosis are not uncommon. The coexistence of peptic ulcer and diabetes is not infrequently observed. In each of these instances the ulcer may bleed and the prognosis be aggravated because of the primary disease.

Relatively few authors have attempted to evaluate the part played by complications and by associated diseases in the death rate from bleeding peptic ulcer, but study of the scant number of autopsies reported makes it evident that this is an important aspect of the clinical problem.

<sup>12</sup> WANGENSTEEN, O. H.: The ulcer problem, *Jr. Canad. Med. Assoc.*, 1945, liii, 309.

<sup>13</sup> GOLDMAN, L.: Gross hemorrhage from peptic ulcer, *Jr. Am. Med. Assoc.*, 1935, cvii, 1537.

<sup>14</sup> KINNEY, T. D., and MALLORY, G. K.: Cardiac failure associated with acute anemia, *New Eng. Med. Jr.*, 1945, ccxxxii, 215.

## REVIEWS

*Fundamentals of Clinical Neurology.* By H. HOUSTON MERRITT, M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Chief of Division of Neuropsychiatry, The Montefiore Hospital; FRED A. METTLER, M.D., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University; and TRACY JACKSON PUTNAM, M.D., Professor of Neurology and Neurological Surgery, College of Physicians and Surgeons, Columbia University. 289 pages; 25.5 × 17 cm. 1947. The Blakiston Company, Philadelphia. Price, \$6.00.

The authors, who are outstanding leaders in the fields of clinical neurology, neuro-anatomy and neuro-surgery, have produced in this short (289 pages) monograph an excellently condensed review of the whole field of clinical neurology. It is full of excellent plates and diagrams which give function as well as location and name. The examination technics described in the first part of the book are especially useful because the positive findings of various tests are interpreted. The same applies to the description of spinal fluid examination. This book is in no sense an introductory book for beginners. Its main usefulness, as the reviewer sees it, will be for two groups: those who want a quick but complete review in preparation for American Board Examinations; and those medical practitioners who need assistance in the examination and understanding of the patients they encounter who have a disease of the nervous system.

H. W. N.

*Digitalis and Other Cardiotonic Drugs.* By ELI RODIN MOVITT, M.D. 204 pages; 16 × 24.5 cm. Oxford University Press, New York. 1946.

Dr. Movitt has reviewed and abstracted the extensive recent literature pertaining to digitalis and related drugs. For the most part, the abstracts from original articles are detailed enough to convey clearly the author's view. Over 400 papers are analyzed in this monograph. There is fair presentation of opposing opinions on controversial subjects. The arrangement into chapters and the index facilitate ready reference.

The book will be of especial interest to cardiologists, but the general internist will find much of value. It will serve as a valuable reference to all workers in this field.

C. E. L.

## BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Advances in Internal Medicine* (Volume II). Editors: WILLIAM DOCK, M.D., Long Island College of Medicine; I. SNAPPER, M.D., The Mount Sinai Hospital, New York. 642 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, \$9.50.

*Advances in Pediatrics* (Volume II). Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School, Boston; L. EMMETT HOLT, JR., New York University, College of Medicine, New York; A. ASHLEY WEECH, University of Cincinnati, College of Medicine, Cin-

cinnati. 409 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, \$6.75.

*Cancer: Diagnosis, Treatment, and Prognosis.* By LAUREN V. ACKERMAN, M.D., Pathologist to the Ellis Fischel State Cancer Hospital, etc.; JUAN A. DEL REGATO, M.D., Radiotherapist to the Ellis Fischel State Cancer Hospital, etc. 1,115 pages; 25.5 × 18.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$20.00.

*The Causation of Appendicitis.* By A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., Professor of Surgery, University of Bristol, etc. 79 pages; 19 × 12.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, \$2.50.

*Concise Anatomy.* By LINDEN F. EDWARDS, Ph.D., Professor of Anatomy, The Ohio State University, Columbus. 548 pages; 25.5 × 17.5 cm. 1947. The Blakiston Company, Philadelphia. Price, \$5.50.

*Dermatologic Clues to Internal Disease.* By HOWARD T. BEHRMAN, M.D., Assistant Clinical Professor of Dermatology, New York University College of Medicine, etc. 165 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Incorporated, New York. Price, \$5.00.

*Diseases Transmitted from Animals to Man (Third Edition).* By THOMAS G. HULL, Ph.D., Director, The Scientific Exhibit, American Medical Association; and other contributors. 571 pages; 24.5 × 16 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$10.50.

*A Manual of Otology, Rhinology and Laryngology (Third Edition).* By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Associate Professor and Acting Chairman of the Department of Otolaryngology, Northwestern University School of Medicine, Chicago, etc. 352 pages; 24 × 15.5 cm. 1947. Lea & Febiger, Philadelphia. Price, \$4.50.

*Medical Addenda: Related Essays on Medicine and the Changing Order.* By Various Authors. 156 pages; 21.5 × 14 cm. 1947. The Commonwealth Fund, New York. Price, \$1.75.

*Medical Disorders of the Locomotor System, Including the Rheumatic Diseases.* By ERNEST FLETCHER, M.A., M.D. (Cantab.), M.R.C.P., Physician to the Arthritis Clinic and Lecturer on the Rheumatic Diseases, Royal Free Hospital, etc. 625 pages; 25.5 × 16 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$11.00.

*Ophthalmology, being Section XII of Excerpta Medica (A Complete Monthly Abstracting Service of the World Medical Literature Comprising 15 Sections and Covering the Whole Field of Theoretical and Clinical Medicine.)* Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology, University of Amsterdam, etc. 48 pages; 25 × 16.5 cm. (paper). 1947. The Williams & Wilkins Company, Baltimore. Price: Subscription, \$15.00.

*Osteotomy of the Long Bones.* By HENRY MILCH, M.D., Consulting Orthopedist, Maimonides Hospital. 294 pages; 24 × 16 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$6.75.

*Physician's Handbook (Fourth Edition).* By JOHN WARKENTIN, Ph.D., M.D., and JACK D. LANGE, M.S., M.D. 282 pages; 16.5 × 10 cm. (paper). 1946. University Medical Publishers, Chicago. Price, \$1.50.

*Signs and Symptoms: Their Clinical Interpretation.* Edited by CYRIL MITCHELL MACBRYDE, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 439 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$12.00.

*Skin Manifestations of Internal Disorders (Dermadromes).* By KURT WIENER, M.D., Dermatologist, Mount Sinai Hospital, Deaconess Hospital, Saint Michael's Hospital, Milwaukee. 690 pages; 25.5 × 18 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$12.50.

*The Years After Fifty.* By WINGATE M. JOHNSON, M.D., Professor of Clinical Medicine and Chief of Private Diagnostic Clinic, Bowman Gray School of Wake Forest College. With a Foreword by MORRIS FISHBEIN, M.D., Editor, Journal of the American Medical Association. 153 pages; 21 × 14.5 cm. 1947. Whittlesey House, McGraw-Hill Book Company, Inc., New York. Price, \$2.00.

*The Development of Modern Medicine: An Interpretation of the Social and Scientific Factors Involved.* By RICHARD HARRISON SHRYOCK. 472 pages; 22 × 15 cm. 1947. Alfred A. Knopf, Incorporated, New York. Price, \$5.00. (Revised edition.)

## COLLEGE NEWS NOTES

### RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948–June 30, 1949. The Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from \$2,200 to \$3,000.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

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### ADDITIONAL LIFE MEMBERS

The College takes great pleasure in announcing that the following Fellows, listed in the order of their subscriptions, have become Life Members of the College.

Stanley T. Simmons, Louisville, Ky., June 27, 1947

Louis F. Bishop, Jr., New York, N. Y., June 30, 1947

Ricardo Aguilar Meza, Tiquisate, Escuintla, Guatemala, July 8, 1947

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### SUPPLEMENT TO 1947 MEMBERSHIP ROSTER DISTRIBUTED

A Supplement to the 1947 Membership Roster, designed to bring the membership list up to date as of August 1, 1947, has now been published and distributed to all members of the College in good standing. If any have failed to receive their copies, or have noted any corrections or omissions in the Supplement listings, they are requested so to inform the Executive Secretary of the College.

The Supplement records all elections at the 1947 Annual Session. It contains also the full Constitution and By-Laws, as amended on May 1 at the Session.

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### TWENTY-NINTH ANNUAL SESSION—SAN FRANCISCO, CALIF.

The 29th Annual Session of the College will be held in San Francisco, April 19–23, inclusive, 1948, with General Headquarters at the Civic Auditorium. No single hotel has adequate facilities to accommodate a large proportion of the members, but fully adequate hotel accommodations are available for everyone. The College will publish a list of "Official Hotels" and members may make reservations directly by identifying themselves with the College and with this meeting.

As President of the College, Dr. Hugh J. Morgan, Vanderbilt University Hospital, Nashville, Tenn., is responsible for the program of Morning Lectures and afternoon General Sessions. Dr. William J. Kerr and Dr. Ernest H. Falconer, of San Francisco, are Co-General Chairmen, and through them and their Committees, the pro-

## Tentative Outline of San Francisco Session

Time	Monday April 19	Tuesday April 20	Wednesday April 21	Thursday April 22	Friday April 23
9:00 a.m. to 11:30 a.m.	Morning free. Registration, Exhibits, etc.	Hospital Clinics	* Morning Lectures (9:30-11:30)	Hospital Clinics	* Morning Lectures (9:30-11:30)
12:00 m. to 1:15 p.m.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1:15 p.m. to 2:15 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:15 p.m. to 5:00 p.m.	1st General Session	2nd General Session	3rd General Session	Annual Business Meeting — 4th General Session	5th General Session
5:00 p.m. to 8:00 p.m.	Dinner		Dinner	Annual Banquet	
8:00 p.m. to 11:00 p.m.	Entertainment and Opening Reception		Convocation followed by President's Reception		

\* Two simultaneous series.

gram of Clinics, Panel Discussions and Entertainment is being arranged. They have already appointed the following Committee Chairmen:

Dr. Dwight L. Wilbur, Committee on Clinics  
 Dr. Roberto F. Escamilla, Committee on Panel Discussions  
 Dr. Sidney J. Shipman, Committee on Entertainment  
 Dr. William C. Voorsanger, Committee on Hotels and Transportation  
 Mrs. Stacy R. Mettier, Committee on Ladies' Entertainment.

New features will be introduced into the program, among which will be a change in the organizational type of the Meeting. Hospital Clinics and Demonstrations will occupy exclusively two mornings, Tuesday and Thursday; there will be no conflicting Morning Lectures or other program features those two mornings. There will be two simultaneous programs of Morning Lectures on Wednesday and Friday mornings, without other conflicting program features. Panel Discussions, with several new ideas, will be conducted daily, Tuesday through Friday, from 12 m. to 1:15 p.m. The General Sessions will be held daily, Monday through Friday, from 2:15 p.m. to 5 p.m., but there will be no General Sessions in the evening.

It will be the 100th Anniversary of the "GOLD RUSH" and several unique features are being planned.

AUTUMN SCHEDULE OF REGIONAL MEETINGS  
AMERICAN COLLEGE OF PHYSICIANS

Territory	City	Date	General Chairman
Western Pennsylvania	Pittsburgh	September 10, 1947	R. R. Snowden, Governor
North Dakota	Bismarck	September 13, 1947	R. B. Radl, Governor
Oklahoma	Oklahoma City	September 20, 1947	Wann Langston, Governor
Nebraska	Lincoln	September 20, 1947	J. D. McCarthy, Governor
Iowa	Des Moines	September 27, 1947	B. F. Wolverton, Governor
New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont)	Burlington, Vt.	October 14, 1947	Ellsworth L. Amidon, Governor
Western New York	Syracuse	October 28, 1947	E. C. Reifenstein, Sr., Governor
Western Michigan	Muskegon	October 29, 1947	W. M. LeFevre, Chairman
New Jersey	Newark	November 7, 1947	G. H. Lathrop, Governor
Kentucky	Louisville	November 8, 1947	A. J. V. Klein, Chairman
North Carolina	Chapel Hill	November 14, 1947	C. W. Dowden, Governor
			P. F. Whitaker, Governor
			R. L. McMillan, Chairman
Midwest (Illinois, Indiana, Michigan, Minnesota, Wisconsin)	Milwaukee	November 15, 1947	K. L. Puestow, Governor
			F. D. Murphy, Chairman
Eastern Pennsylvania and Delaware	Philadelphia	November 21, 1947	E. L. Bortz, Governor
Florida	Tampa	† December 8-9, 1947	T. Z. Cason, Governor
			W. C. Blake, Chairman

† Followed by a proposed trip to Havana where a Regional Meeting for Cuba will be conducted under Dr. José Centurión, Governor.

NORTH CAROLINA REGIONAL MEETING

The North Carolina Annual Regional Meeting of the American College of Physicians will be held at Chapel Hill, with the University of North Carolina Group acting as hosts, on Friday, November 14. Dr. Paul F. Whitaker, Kinston, is the Governor for North Carolina; Dr. Robert L. McMillan, Winston-Salem, is Chairman of the Program Committee; Dr. Edward McG. Hedgpeth, of Chapel Hill, is Chairman of Local Arrangements.

Fellows and Associates will be chosen very largely for program presentations, and it is predicted that this will be one of the largest and most enthusiastic meetings of the College ever held in North Carolina, which was one of the pioneer states in initiating regional meetings many years ago.

POSTGRADUATE COURSES BY THE AMERICAN COLLEGE OF PHYSICIANS

In the advertising section of this issue of the ANNALS will be found the full schedule of courses offered by the American College of Physicians during the autumn of 1947. Already Course No. 1, Internal Medicine, has been concluded and Course



No. 2, Psychosomatic Medicine, at the University of Colorado, and Course No. 3, Mechanics of Disease, at the Peter Bent Brigham Hospital, Boston, are in progress. The Postgraduate Bulletin, together with detailed course outlines for Courses 1 to 5, were distributed to all Fellows and Associates of the College on August 1. In the meantime, the detailed outlines for the remaining courses have been received and printed and are available on request to the Executive Secretary of the College. The maximum facilities of these courses is 665. Many of the courses will be completely filled by members of the College while in some other courses, accommodations will be available for several qualified non-members.

The Advisory Committee on Postgraduate Courses has probably organized the most attractive postgraduate program this year in the history of the College, and through continued experience the courses improve in quality and grow in popularity.

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#### UNIVERSITY OF CALIFORNIA, LOS ANGELES, OFFERS POSTGRADUATE COURSES

"Lifelong Learning" is the title of a bulletin issued by the School of Medicine of the University of California, Los Angeles, listing Medical Refresher Courses scheduled between September and December, 1947. Courses are offered in Dermatology, Syphilology, Medical Mycology, Serology and Immunology; Gynecology; Otorhinolaryngology; Urology; Medicine; General Surgery; Cardiology; and Pediatrics. The courses will continue one evening per week from 8 p.m. to 10 p.m. over periods of approximately seven weeks, and the fee varies from \$50.00 to \$75.00, except the course in Pediatrics for which the fee is \$25.00.

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#### CHICAGO MEDICAL SOCIETY OFFERS POSTGRADUATE COURSES

The Chicago Medical Society has announced a course in Cardiovascular Diseases, October 20-25, and a course in Gastro-enterology, October 27-November 1, each course limited to 100. The courses are open to all physicians in good standing in their county medical societies anywhere in the United States.

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The Interstate Postgraduate Medical Association of North America will have its 1948 Assembly in Cleveland at the Public Auditorium during the week of November 8, 1948. Further information concerning the program of this Assembly will be published in a later issue.

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Dr. Robert F. Loeb, F.A.C.P., New York, has been appointed Bard Professor of Medicine in the Columbia University College of Physicians and Surgeons, as well as Director of Medical Service in the Presbyterian Hospital. Dr. Loeb succeeds in this position Dr. Walter W. Palmer, President-elect of the College.

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Dr. Lowell T. Coggeshall, F.A.C.P., Chicago, has been appointed to succeed Dr. R. Wendell Harrison as Dean of the Division of Biologic Sciences of the University of Chicago. This division includes the School of Medicine. Dr. Coggeshall also holds appointment as Professor of Medicine and Chairman of the Department.

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Dr. Ross T. McIntire, F.A.C.P., Washington, D. C., formerly Surgeon General of the U. S. Navy, has been appointed Director of the American Red Cross' National Blood Program. In this position Dr. McIntire will supervise collection of an estimated 3,700,000 blood donations annually at strategically located centers throughout

the country. It is the purpose of the program to make available adequate supplies of whole blood and plasma and, in addition, the newer blood derivatives which have been developed largely during the war years. Such a program, conceived on a national scale, will utilize civic donor centers with mobile units to cover outlying communities. It is planned to utilize existing hospitals in the distribution of blood and blood fractions.

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Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif., has been honored by the award of the Gold Cross of the Royal Order of Phoenix by the Greek Government.

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Dr. Peter J. Steincrohn, F.A.C.P., Hartford, Conn., has generously donated to the College Library of Publications by Members a copy of his new book, "What You Can Do for High Blood Pressure," published by Doubleday & Co., N. Y.

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On September 1 Dr. Tom D. Spies, F.A.C.P., who has been Associate Professor of Medicine in the University of Cincinnati and has directed that University's nutritional investigations at the Hillman Hospital, Birmingham, Ala., will become Professor of Nutrition and Metabolism in the Northwestern University School. Northwestern University has created a new department in this field and Dr. Spies will have charge of it. He will continue his studies at the Hillman Hospital.

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The Typhus Commission Medal has been awarded to Dr. Joseph F. Sadusk, Jr. (Associate), New Haven, Conn. This award recognizes Dr. Sadusk's important contributions to the study of scrub typhus while Executive Officer of the Special Commission in the Southwest Pacific in 1943.

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Dr. Henry Pleasants, Jr., F.A.C.P., West Chester, Pa., has contributed to the College Library of Publications by Members a copy of his recent autobiographical book, "A Doctor in the House," which was published by J. B. Lippincott Co., Philadelphia.

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Dr. R. E. Beamish (Associate) of the Manitoba Clinic, Winnipeg, Manitoba, Canada, has been awarded a Nuffield Foundation Traveling Fellowship for study in Great Britain and is now located in London.

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#### JOINT COMMITTEE FOR THE COORDINATION OF MEDICAL ACTIVITIES

The Joint Committee for the Coordination of Medical Activities, successor to the Committee on Post-War Planning for Medical Service, composed of representatives from the American Medical Association, the American College of Surgeons, the American Board for Medical Specialties, the American Dental Association, the American Hospital Association, American Pharmaceutical Association, Association of American Medical Colleges, the Veterans Administration, Office of the Surgeon General of the U. S. Army, the Bureau of Medicine and Surgery of the U. S. Navy, and several other organizations, is continuing its sessions during 1947, having held its last meeting at the A. M. A. Headquarters, on August 16, 1947. Among subjects on the agenda were:

Hospital Residencies and Graduate Education, by Dr. Donald Anderson;  
Licensure, with particular reference to graduates of foreign extramural schools,  
by Dr. W. L. Bierring;

Report of the Subcommittee on a Specialty Board for General Practitioners;  
Report of Subcommittee on Legislation for a National Department of Health;  
Hospital Survey and Construction Program, by Miss Mary Switzer;  
Shortage of Nursing Personnel, by Mr. Graham L. Davis;  
Training of Practical Nurses, by Father Schwitalla;  
New A. M. A. Committee on Nursing Problems;  
The Navy Educational Program, by Capt. W. E. Eaton;  
Rural Medical Service, by Dr. H. B. Mulholland;  
A Progress Report on American Red Cross Blood Bank Program, by Dr. W. F. Draper.

Minutes of the Meeting will be published in the Journal of the American Medical Association.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to July 14, 1947 inclusive).

Edward S. Brewster, Boone, Iowa (Lt. Col., MC, AUS)  
Vincent Del Duca, Camden, N. J. (Capt., MC, AUS)  
Robert E. Driscoll, Chicago, Ill. (Capt., MC, AUS)  
George M. Edwards, Russellville, Ky. (Col., MC, USA)

*OBITUARIES*

## DR. ALEXANDER W. WINKLER

Alexander W. Winkler, M.D., F.A.C.P., New Haven, Connecticut, died on June 26, 1947, at the age of 38.

Dr. Winkler was born November 20, 1908, in Ann Arbor, Mich. He received his B.A. degree from the University of Michigan in 1927 and his M.D. degree from Harvard Medical School, in 1931. Following an internship at Johns Hopkins Hospital he held a research fellowship at the Thorndike Memorial Laboratories, Harvard Medical School. In 1933 he came to New Haven, Conn., to become associated with the Yale University School of Medicine and the New Haven Hospital, advancing to the position of Assistant Professor of Medicine in 1941, which he held at the time of his death.

In addition to his work as an able clinician and teacher, Dr. Winkler had achieved distinction as an investigator in the fields of physiology and biochemistry as well as clinical medicine. The author of numerous scientific papers, his most notable contributions dealt with the metabolism of water and salts, diseases of the thyroid and diabetes.

He was a Fellow of the American Medical Association and a member of the American Society for Clinical Investigation, the American Diabetic Association, the American Physiological Society and the Interurban Clinical Club. He was also a member of three honorary societies: Phi Beta Kappa, Alpha Omega Alpha and Sigma Xi.

His death at an early age is a great loss to medicine.

FRANCIS G. BLAKE, M.D., F.A.C.P.

## DR. ARCHIE MARVIN ROBERTS

Dr. Archie Marvin Roberts was born in Brandon, Texas, on August 2, 1902. He received his Bachelor of Arts degree at the University of Southern California in 1924, and graduated from Stanford University School of Medicine in 1929. After postgraduate study at Tulane University and Stanford Medical Schools, he entered private practice in Los Angeles in 1932. He was a diplomate of the American Board of Internal Medicine, 1938, became a Fellow of the American College of Physicians in 1942, and thereafter became a Life Member. He was a member of Stanford Chapter of the Society of Sigma Xi and Alpha Omega Alpha. He was a member of numerous local and national medical societies, and took an active part in all projects which would raise the standard of the practice of medicine in this area.

Dr. Roberts was Assistant Professor of Medicine at the University of Southern California Medical School, and had been President of the Los Angeles Heart Association from October, 1944, until the time of his death.

Dr. Roberts was a forceful member of many welfare organizations, and was a member of the Board of Directors of the Los Angeles County Tuberculosis Association. He was one of the most respected members of the medical profession in Southern California. His untimely death which took place suddenly on April 1, 1947, following an atypical pneumonia, was a great shock to all of his friends and colleagues.

LELAND HAWKINS, M.D., F.A.C.P.,  
Governor for Southern California

### DR. HAROLD FOSTER DUNLAP

The death of Dr. Harold Foster Dunlap, age 51, of Indianapolis, on July 22, 1947, is a great loss to the medical profession of Indiana. He was a highly trained physician in his special field of internal medicine and diagnosis.

Dr. Dunlap was born at Duncannon, Pa., the son of the Reverend Wilton and Irene (Beck) Dunlap. He received a Bachelor of Science degree at Indiana University in 1918, a Doctor of Medicine degree from the Indiana University School of Medicine in 1920, and a Master of Science in Medicine degree from the University of Minnesota in 1929. He served his internship at the Philadelphia General Hospital in 1920-22, and was a Fellow in Medicine at the Mayo Clinic, Rochester, Minn., in 1925, and a Consultant in Medicine there from 1925 to 1932. He was a diplomate of the American Board of Internal Medicine.

Dr. Dunlap was a member of the staffs of the Methodist, St. Vincent's and Indianapolis City Hospitals. He formerly was Chief of Medical Service at the City Hospital and served on many boards and committees of hospitals in Indianapolis. He had practiced in Indianapolis fourteen years, with an office at 723 Hume Mansur Bldg.

Dr. Dunlap was a member of the Lutheran Church, Phi Beta Pi Fraternity, the American Medical Association, the Association for Study of Internal Secretions, the Blockley Medical (Philadelphia) Alumni Association, the Mayo Foundation, and became a Fellow of the American College of Physicians in 1934. He was chairman of the medical advisory board of the Indiana Selective Service Commission and served on the Marion County Board of Appeals five years.

Dr. Dunlap's portrait is on file in the Army Medical Library, Washington, D. C., as a person prominent in the field of medicine.

ROBERT M. MOORE, M.D., F.A.C.P.,  
Governor for Indiana

# ANNALS OF INTERNAL MEDICINE

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## THE PROBLEM OF THE NEUROTIC PATIENT \*

By WILLIAM C. MENNINGER, M.D., F.A.C.P., *Topeka, Kansas*

THE title of my paper, "The Problem of the Neurotic Patient," does not make clear whether the patient or the doctor has a problem. Actually they both have: to the patient his neurotic illness is a problem, to the doctor the diagnosis and treatment of that illness are often a problem.

As a psychiatrist, I represent a minority of the medical practitioners. However, the subject of my discussion, "the neurotic patient," represents a majority of all of the patients who seek help from physicians. This fact is not new but military experience gave dramatic evidence to support it. The discharges with neuropsychiatric diagnoses alone accounted for more than the total of those given for infections, disorders of the gastrointestinal, cardiovascular, respiratory and genito-urinary systems, for ear, eye, nose and throat afflictions, tuberculosis and venereal disease. Considerably more than half of the neuropsychiatric discharges were for psychoneuroses and undoubtedly many neurotic soldiers were discharged under other diagnoses. For every man medically discharged, there is statistical evidence that at least five other men were seen by a psychiatrist for some type of personality disorder which did not lead to discharge. In addition, 150,000 soldiers were discharged through administrative rather than medical channels because of personality difficulties.

This information can be interpreted variously and each interpretation will include some part of the total explanation. It surely reflects the fact that Army life was difficult and exacting and that our way of living had not prepared many American youths for such demands. It probably indicates a critical state of affairs in the American family. It might be construed as evidence of some kind of inadequacy in our system of practicing medicine, and, therefore, as a failure in our medical education. Certainly, it was a disturbing indication of the extent of temporary or existing mental ill health.

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\* Presented at the Twenty-Eighth Annual Session, American College of Physicians, Chicago, April 28, 1947.

The picture we saw in the Army must exist in modified form in civilian life, since our soldiers were primarily civilians. In any event it presents a major challenge to American medicine upon which the health, both mental and physical, of our people depends.

Most doctors will agree that a high percentage of their patients present emotional problems which either cause or complicate a clinical picture. The family physician of yesteryear who came to the home to see his patient also saw the family relationships as he lingered for a chat over a cup of coffee. He heard about daughter's love affair and son's job, mother's over-work and father's worry. Along with sugar pills, his interest and advice were part of the treatment rendered. Now a doctor sees the patient in the more formal atmosphere of an office or in the hospital. Scientific data have accumulated to such an extent that no one physician can keep abreast of the new technics and skills essential for a "general practice." Consequently, some of us concentrate on trying to be expert in a part of the total field. In such a highly specialized profession we lose contact with each other. We often do not have time or take time to "just listen" to the patient and then evaluate the rôle of the emotional factors in his illness.

Research and experience, while contributing to our knowledge of the reaction of organs and bacteria to new forms of therapy, have also led to greater understanding of the management and prevention of mental illness. Of particular importance is the increasing appreciation of the presence of an emotional factor in all illness. Physicians are looking more and more for knowledge of ways and means to neutralize the emotional provocation of organ dysfunction. Psychiatrists are eager to contribute to other doctors, information gleaned from their study of the seriously disintegrated personality as to what factors help maintain emotional balance and what interfere with it.

We have learned that frequently the patients with prodromal symptoms of serious mental illness are seen first by the laryngologist, the orthopedist, the endocrinologist or the internist. Too often, only when the symptoms become psychologically incapacitating are they brought to the attention of the psychiatrist. Only then is their neurotic reaction diagnosed primarily as such. In many such cases the first doctor consulted by the patients might have aborted or relieved the symptoms. In many other cases earlier referral might have given a better outlook in treatment.

Since neurotic reactions are so complicated, it is neither practical nor pertinent here to attempt a review of their classification nor the details of their pathology. The many positive or negative points about their treatment are necessarily based on the pathology. Consequently these cannot be condensed in this brief presentation even if that were desirable.

Our understanding of that form of emotional illnesses—"the neurosis"—has increased greatly during the last 20 years. But much of this information has not become common knowledge either to our physicians or to our

medical students. Some of us in the Army were impressed repeatedly with the fact that a majority of physicians lacked a working understanding of this large area of medicine. We can lay the blame of this ignorance on improper medical education, on our over-emphasis on mechanical and chemical diagnostic aids, on the intangible quality of emotions or on our still incomplete knowledge of psychiatry. However, to place the blame helps little unless it leads to the correction of our inadequacy. Perhaps touching briefly on some of the deficiencies observed in the Army may be helpful.

Many physicians are quite unable to give any scientific explanation for an hysterical paralysis, a phobia of tuberculosis, or of a so-called organ neurosis. They know that the action of the heart or lungs is involuntary but they have difficulty in recognizing and accepting as valid the fact that a major portion of the personality is not under voluntary control. They have not learned to feel at home with a knowledge of the structure and the function of the personality which includes the basic concept of the existence of an unconscious. Just as jaundice is described in reference to the anatomy and physiology of the liver, a neurotic symptom can be explained only in terms of the anatomy and physiology of the personality.

The psychiatrist considers the unconscious as a major area of the personality function. We make no attempt to structuralize or to locate it anatomically. It is the source of one's life energy, instincts and primitive drives. The unconscious contains at birth the psychological heritage of the organism which is characteristic of his species. It stores the accretions of the individual's development—the forgotten experiences and memories and all of the urges to forbidden activities and desires which are repressed because of parental influence, training, experience, social demands and culture.

From birth through the first years of life the growing child develops a conscious personality through which he maintains contact with his environment. It is a function of this consciousness to attempt to control the primitive energy and instincts which the infant brought into the world with him. As he becomes a mature individual, he learns that society demands that he censor and direct the superior power and drives of the unconscious. To the conscious portion of the personality belongs the responsibility for seeing that the expressions from the unconscious conform to socially acceptable standards and approval.

The mentally healthy personality is able to control the unconscious drives for expression. Nevertheless, even in the well integrated person, their pressure to find an outlet may temporarily overcome all modifications of or defenses against their expression—perhaps in sleep, under the influence of alcohol, as a result of fatigue, in the course of a fever. Or the unconscious drives may gain more permanent expression in the disguised forms which we label neurotic symptoms.

Usually the first indication that the conscious personality cannot control the threatened escape of a primitive impulse or urge is a feeling of anxiety.



This anxiety or uneasiness is a danger signal of an impending threat to self-control. Just as in all biologic phenomena, the organism tries to heal itself. In the case of anxiety, the personality mobilizes its resources to prevent the escape of the impulse. The apprehensiveness, restlessness or fearfulness which are expressions of a conflict between unconscious pressure and conscious control can be resolved sometimes by changes in the environmental situation. Sometimes the conflict can be resolved if the individual gains a better understanding of the factors in his situation to which he is reacting. If the conflict is not resolved, the personality is forced to utilize some type of automatic defense, of which there are many forms.

One defense is to channel the initial impulse into symptom expression—some disturbance of gastrointestinal or cardiovascular function, curiously distorted fears, bizarre compulsive behavior, affections of motor or sensory or visceral functions, or any other so-called “neurotic” symptom. These represent a socially approved escape for the disapproved impulse. What is very important to understand is that the individual himself is no more capable of voluntary control of such symptom formation than of the rate of his heart beat. Such symptoms represent the basic energy drives and appear as involuntarily and as automatically as do one’s changes in peristaltic action. Since the initial impulse was unconscious the patient cannot explain its expression. At best he can offer only a superficial rationalization which he himself may regard as inadequate. These are neurotic symptoms.

Each symptom, because it represents a kind of triumph of the powerful unconscious over the conscious control, is a distorted form of gratification. Simultaneously, however, these symptoms are painful and thus they serve as a punishment inflicted by one part of the personality upon another part of it for permitting the escape of a forbidden impulse.

This complicated phenomenon is far too simplified in the above explanation. At times everyone manifests such neurotic symptoms. They do not represent ill health any more than does the minor impairment of any other biological system. Many individuals, although they remain productive and creative, exist continuously only at a level of neurotic adjustment. In other words, the struggle within them is never resolved. Their defenses which are mobilized against the release of the denied impulse, are conspicuous. They show eccentricities or strange mannerisms, curious personal habits or unusual forms of behavior. Strange philosophies or a long suffering wife or husband give them unseen supports in the struggle between their personalities and the world in which they live. When their routine is not grossly disturbed, they are not incapacitated.

When the defenses break down sufficiently so that neurotic symptoms cause incapacity, a diagnosis of some type of neurotic reaction is justified. Sometimes this may be an acute decompensation such as occurred during the war in combat in previously well integrated individuals. It occurs too, not infrequently, in civilians who are under acute emotional stress. On the

other hand, there is the slow cumulative decompensation seen most clearly in the chronic neurotic invalid.

Neurotic reactions are not so simple, however, as to be merely the partial or distorted escape of a primitive impulse from the control of the conscious. The personality is far more complicated. It includes all that the organism starts with—the germ plasm of a given inheritance—plus all of the experiences of his life. In most, if not in all neurotic reactions, a major etiologic factor will be found in a disturbance in the development of the personality.

In both acute and gradual decompensation, severe neurotic symptoms are traceable to psychological injury during infancy and early childhood. Patterns of relationship to the environment, and more particularly to the people in that environment, are established during early life. Then the organism is particularly sensitive, and therefore vulnerable, to traumatic events. The personality of every adult bears some scars of emotional injuries in childhood. Close psychiatric scrutiny will reveal the evidence of drouths, blights, floods and sunny weather experienced by a personality during its development. A deeper scar, resulting from a particularly traumatic event, represents a specially weak spot—an Achilles heel—which is more subject to later damage by an experience in adulthood similar to the one which caused the childhood scar. Under ordinary life situations, such weaknesses are not apparent either to the individual or to the observer.

We see wide variations in the type and degree of reactions of different individuals to the same situation. This fact is apparently confusing to many physicians. They recognize very well that a typhoid inoculation may produce a violent reaction in one individual and no reaction in another. Consequently, it should not be surprising that a particular emotional experience may produce an extremely neurotic reaction in one person but not in another. However, this phenomenon is often interpreted as being faked by the first person, on the basis that it did not produce the same reaction in a second person. It is not easy to explain the varying responses either to the typhoid inoculation or to the emotional stress but both are valid, scientific observations. As a matter of fact, it is probably easier to explain the emotional response than the typhoid response.

Too many doctors also seem unable to accept the validity of a neurotic illness, perhaps because of the scotoma for this field in their medical education. Since they have been taught that illness is physical, a neurotic illness is a paradox because there may be no physical findings, or the physical findings obviously do not explain the complaints. Lacking psychiatric orientation, these physicians have no basis for understanding the phenomena they see. They use the mechanical and chemical diagnostic aids with which they are familiar—the laboratory, the roentgen-ray, the electrocardiograph. In the absence of positive findings, they repeat the examination or search for another source of trouble. They may conclude that the problem is psychological but withdraw in the face of ignorance of suitable treatment methods.

They were taught how to give drugs and prescribe diets but very few medical students—or doctors—have received either formal or informal instruction in the most important therapeutic tool in all medicine—psychotherapy.

The intangibility of psychopathology in contrast to the visual evidence of physical pathology creates a kind of anxiety in some physicians. One of his responses is seen in the over-examination of a neurotic patient. If this process were harmless, there might be less reason for concern. Instead, as a rule, it intensifies and tends to fix the neurosis. The findings of an examination are impressive to the patient, especially if explained by the physician with an air of great seriousness. Even a minor physical finding can be used by the patient to justify his illness as a "real" (physical) one and enable him to escape the recognition that it is psychological. It should become axiomatic that one cannot compensate for a lack of understanding by making repeated physical or chemical examinations. The technic of making a diagnosis by elimination is rarely justified.

There are many approaches to the examination of the personality. Just as a physician does not merely accept the word of his patient that he has kidney disease, neither should he accept at face value the patient's statement that he has a psychoneurosis. The physician is, or should be, curious as to why the patient thinks he has a particular symptom. He must go further and look for pathology within the troublesome body system. One step preliminary to making a diagnosis of disease of the kidney is an examination of its product. *Before mental illness can be diagnosed an investigation of the expressions of the mind and emotions is essential.* Just as analysis of the urine may reveal the presence of pathology, an analysis of the emotional products of the mind, e.g., hostility, is an essential examination to reveal pathology of the personality.

The present day physician's attitude toward and understanding of most mental excretions is at about the same point as was the attitude of the medical profession to urine analysis 100 years ago. At that time a few curious physicians looked at it; a very few more brave ones tasted it.

Currently physicians rarely inquire about hate or resentment unless the patient forces this on their attention. Even then they are prone to regard these as unrelated to his heart complaint. Just as physicians have learned that the excretion, urine, is a very important lead to pathology, they will learn to recognize hostility as another kind of an excretion that usually indicates gross pathology. For instance, deep resentment or hatred towards some close associate is always indicative of serious conflicts within the individual's psychological life and may be reflected in many varied symptoms. The presence of strong hostilities should lead to certain diagnostic tests of the personality. These, in turn, would need to be correlated with a study of the psychological metabolism: an evaluation of the intake, the deficiencies or excesses of all the major interpersonal relationships in the individual's life, his loves and his hates and their variations. Medicine has given lip

service, without real conviction, to the idea that we physicians should treat the patient "as a whole," to "comprehensive medicine," or that we should treat the person and not his disease. The fact is that a considerable portion of American physicians still are treating just the disease.

The neurotic patient cannot cure himself. Too often, however, the physician's own personal observation is that there is really nothing wrong with him. In fact, we saw thousands of instances in the Army where the physician so told the patient, though in private practice he is not as likely to do so. Many physicians, however, not knowing what else to do, resort to giving placebos or platitudes. Neurotic patients can help themselves in their recovery, but only after the doctor has stepped into their environment and helped them reestablish their equilibrium. He does this by helping the patient reorient himself, both to his internal psychological conflicts and the external environment. Sometimes he must aid in manipulation of that environment. The necessity to have the assistance of a second party, the physician, is due to the fact that the neurotic patient's difficulty is beyond his own control. He needs the help of someone in whom he has faith and confidence, who understands him, who will be patient with him and who will explain him to himself. Only then can he have the courage or the will power to examine his own psychology and thus aid in his own improvement.

The neurotic patient is indeed a very real problem to the average doctor. He presents a special challenge to medicine which for so long has failed to aid him. Our tempo of life with its increasing stresses and strains may be expected to produce even more neurotic symptoms in apparently well people. At the same time, the war's toll in psychoneurotic casualties has increased the awareness of both physicians and laymen of the emotional factors in all disease.

One cannot now help but sense the pulse of increased public interest in mental illness as it has been recently catered to by innumerable articles in national magazines about the neuroses or psychosomatic medicine or psychoanalysis or psychiatry.

This newly awakened interest is a challenge to all medical men. Our Army experience leaves no doubt whatever that the existence of emotional problems in the daily lives of many people is the stimulus for so many feature articles in magazines. It becomes a joint responsibility of all medicine, since certainly 90 per cent of such cases must be handled by the physician to whom the patient goes first, whether he is a general practitioner or a specialist. To prepare himself to handle the problem well, however, the average doctor must take the initiative to acquire the basic facts about the anatomy and physiology and pathology of the personality.

# STREPTOMYCIN IN THE TREATMENT OF MENINGITIS: REPORT OF 27 CASES TREATED AT THE BOSTON CITY HOSPITAL \*

By TOM FITE PAINE,† RODERICK MURRAY, ALBERT O. SEELER and  
MAXWELL FINLAND, F.A.C.P., *Boston, Massachusetts*

CASES of meningitis due to *Mycobacterium tuberculosis* or to gram-negative bacilli are not particularly frequent. They are nevertheless of great importance because of their high mortality and their failure to respond to the various types of therapy, including sulfonamides and penicillin, which have given favorable results in the coccal infections. Only a few reports are as yet available on the results of streptomycin therapy in these types of cases. These reports will be summarized briefly and the results in 24 cases of meningitis due to gram-negative bacilli and in three cases of tuberculous meningitis, that were treated at the Boston City Hospital ‡ will be presented in this paper.

The incidence of meningitis due to various gram-negative bacilli and to the tubercle bacillus as given by various authors is shown in table 1. Such cases occur more frequently in children than in adults. Of the gram-negative bacilli, *Hemophilus influenzae* is the one which causes meningitis most frequently. The results in cases due to this organism will be considered first.

## MENINGITIS DUE TO *HEMOPHILUS INFLUENZAE*

This condition occurs largely in infants and small children, particularly during the first two years of life. Strains of *H. influenzae* are of two main varieties: one a smooth, encapsulated and presumably virulent form and the other a rough non-encapsulated and avirulent form. The rough or so-called "respiratory" strains are occasionally implicated as the cause of meningitis, but they usually are found as normal saprophytic inhabitants of the upper respiratory tract of man. The smooth, encapsulated variety, on the other hand, is found mostly in cases of meningitis. In addition to its presence in meningitis, the latter may be found in the respiratory tract usually in conjunction with acute respiratory infections.<sup>13, 14, 15</sup> During respiratory infections the rough form may undergo transformation to the smooth variety.<sup>16</sup> There are six known serological types among the smooth strains of *H. in-*

\* Received for publication June 9, 1947.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

With the technical assistance of Clare Wilcox.

Aided by a grant from the United States Public Health Service.

† Research Fellow, American College of Physicians.

‡ The patients were under the care of the resident and attending staffs of several different services. The authors are indebted to them all for their interest and cooperation.

TABLE I

Incidence of Meningitis Due to Gram-Negative Bacilli and *Mycobacterium tuberculosis*

Authors	Cases of Meningitis	Organisms			
		<i>Hemophilus influenzae</i>	Coliform Organisms	Other Gram-Negative Bacilli*	<i>Mycobacterium tuberculosis</i>
<i>All Ages</i>					
Neal (1935) <sup>1</sup>	3178	142	8	11	986
Tripoli (1936) <sup>2</sup>	468	20		4	51
Rhoads et al. (1940) <sup>3</sup>	459	29			158
Ferguson and Barr (1944) <sup>4</sup>	72	2	1		6
Rhoads (1947) <sup>5</sup>	550	15	2		16
Brainerd and Bradley (1947) <sup>6</sup>	265	7	5		14
Total	4992	215 (4.3%)	16 (0.32%)	15 (0.30%)	1231 (24.7%)
<i>Infants and Children</i>					
Fothergill and Sweet (1933) <sup>7</sup>	705	78	9	1	290
Lindsay et al. (1940) <sup>8</sup>	642	100		2	205
Silverthorne (1943) <sup>9</sup>	1100	153			368
Neal (1935) <sup>1</sup> (under 3 years)	1077	92	6	4	440
Total	3524	423 (12.0%)	15 (0.43%)	7 (0.20%)	1303 (37.0%)
<i>Autopsies</i>					
Keefer (1941) <sup>10</sup>	83	9			9
Hertzog (1945) <sup>11</sup>	377 (149)†	43 (39)†	10 (9)†	1	56 (16)†
Pote and Courville‡ (1945) <sup>12</sup>	100‡	7§	4§	2	2
Total	560	59 (10.5%)	14 (2.50%)	3 (0.41%)	67 (12.0%)

\* Includes *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, typhoid-dysentery organisms, *Proteus morgani* and others.

† Number of cases under 3 years old.

‡ Meningitis complicating disease of the nose, accessory nasal sinuses or ears.

§ Certain of these were mixed infections, including one case with *Aerobacter aerogenes* and a streptococcus.

*fluenzac*.<sup>17-20</sup> The type b strains account for over 90 per cent of cases of influenzal meningitis.<sup>20, 21</sup>

The predominance of the disease during the first two years of life may be related to the low bactericidal action of infants' blood against *H. influenzae*, type b, as shown by Fothergill and Wright.<sup>22</sup> The common history in these patients is that of an upper respiratory infection followed by the onset of meningitis. It is assumed that in most cases the organisms reach the meninges by the blood stream following invasion through the respiratory tract. Although *H. influenzae* meningitis is usually a "primary" disease of the meninges, cases of infection may certainly occur by extension from foci of infection in the nasal accessory sinuses and ears or may follow fractures involving these areas.<sup>12, 23</sup>

The use of combined sulfonamide and type specific rabbit antiserum in the treatment of meningitis due to *H. influenzae* type b has resulted in a marked lowering of the over-all mortality rate, from nearly 100 per cent to

as low as 7 per cent.<sup>24</sup> The latter figure, however, is based on the results obtained in one series of 28 cases and other authors have reported higher mortality rates up to 50 per cent, with this therapeutic regime.<sup>8, 25-28</sup> Among the drawbacks to serum therapy in this disease are: (1) Type b antiserum, the only type available, is ineffective if the causative organism is not of this type. (2) The incidence of serum reactions is high; they occurred in 12 of one group of 27 patients and there were two instances of severe anaphylactic reaction in that small series.<sup>24</sup> (3) The cost is high and the antiserum is not generally available.

Penicillin has usually been considered ineffective against *H. influenzae* and it was first used as an aid in the isolation of that organism.<sup>29</sup> It has, therefore, not been given an adequate therapeutic trial in cases of meningitis due to this organism. A number of strains of *H. influenzae* isolated from cases of human infection have been tested for sensitivity to penicillin and the majority of smooth strains were found to be completely inhibited by 1.5 units per ml. or less.<sup>30, 31</sup> Rough strains, however, usually required 2.5 to 5.0 units of penicillin per ml. for complete inhibition and some were not inhibited by 5.0 units per ml.<sup>31</sup> Penicillin X is somewhat more effective than penicillin G.<sup>30</sup> Zinnemann<sup>32</sup> treated 15 cases of *H. influenzae* meningitis with combined sulfonamide and penicillin therapy and eight of these patients recovered. Antiserum was used in only one of these cases and that patient died. The course of the illness in these cases was protracted and relapses were frequent after the therapy was stopped. Others have reported cures from the use of sulfonamides and penicillin in a few cases.<sup>33-37</sup>

Drysdale et al.<sup>36</sup> reported the case of a 20-month old infant who was treated for nine days with sulfonamides and penicillin intramuscularly and intrathecally and cultures of the cerebrospinal fluid remained positive for *H. influenzae* type b. At this point the sulfonamides were discontinued and thereafter penicillin alone was given for about one month. The dosage of penicillin was increased from 100,000 to 500,000 units daily by intramuscular injection and the daily intrathecal dose was increased from 25,000 to 50,000 units for a few days and later changed back to 25,000 units. Cultures of the cerebrospinal fluid were negative after the seventh day on this penicillin dosage. The organism in this case was completely inhibited by 0.7 unit of penicillin per ml., and was found to be insensitive to six different sulfonamides. The penicillin concentration in the cerebrospinal fluid 24 hours after an intrathecal injection of 50,000 units of penicillin and while the patient was receiving 500,000 units intramuscularly daily ranged from 1 to 2 units per ml. However, with the same intramuscular dose of penicillin and 24 hours after the intrathecal injection of 25,000 units of penicillin, the concentration in the cerebrospinal fluid varied from 0 to 1.5 units per ml., with an average level of 0.6 unit per ml. which was less than the minimum inhibiting (complete) concentration of penicillin for this particular organism. Accordingly these authors advise doses of at least 50,000 units of penicillin intrathecally daily in cases of influenzal meningitis.

Inasmuch as certain conditions may arise in the treatment of meningitis due to *H. influenzae* which necessitate a change of therapy the possible usefulness of penicillin should be borne in mind.

Streptomycin is effective against *H. influenzae* in vitro and in experimental infections.<sup>30, 39</sup> The sensitivity of most strains ranges from 1 to 5 units per ml.,<sup>40</sup> concentrations that are easily obtained with therapeutic doses in man.

A number of authors have reported on the effectiveness of streptomycin in cases of meningitis due to *H. influenzae*.<sup>41-52</sup> Among the 100 cases cited in the report of the National Research Council<sup>53</sup> there were 17 deaths. These cases cannot be considered as adequately reflecting the value of streptomycin since other agents were also used in a large proportion of them and the streptomycin was often used only after the other therapies had failed.

On the basis of published reports, the chief hazards of streptomycin treatment in *H. influenzae* meningitis are: (1) the development or appearance of streptomycin resistant strains of *H. influenzae* during treatment and (2) the occurrence of complicating secondary infections due to streptomycin insensitive organisms.

Streptomycin resistant strains of *H. influenzae* have been noted to appear during therapy in five of the patients with meningitis that have been reported to date.<sup>42, 46, 49, 52</sup> These cases are of special importance and some of the details are of interest.

One of the patients reported by Alexander et al.<sup>49</sup> was given a single initial intrathecal injection of 25,000 units of streptomycin and none was given by this route again until the fourth day of treatment. At this time a streptomycin resistant strain of *H. influenzae* was present in the cerebrospinal fluid despite the fact that intramuscular streptomycin had been administered throughout the period. The streptomycin was begun early in the disease in this case. In another patient who developed a streptomycin-resistant strain of *H. influenzae* during therapy the disease had been present for a period of two weeks or longer before the streptomycin was started.<sup>49</sup>

In the patient reported by Birmingham et al.<sup>42</sup> therapy with streptomycin was begun late,—on the eighth or ninth day of disease. Following the daily administration of 240,000 units intramuscularly and 20,000 units intrathecally there was some improvement clinically. After the second day, however, the course was downward, cultures of the cerebrospinal fluid yielded a resistant organism and the infant died despite the additional use of antiserum and sulfadiazine.

In the case reported by Morgan and Hunt<sup>46</sup> a streptomycin resistant strain of *H. influenzae* appeared during therapy of a child who already had cerebral abscesses as well as meningitis when treatment was started.

It should be noted that resistant organisms appeared in three patients in whom streptomycin was begun late in the course of the disease and in a fourth case in which treatment was begun early, but the intrathecal injections were interrupted.

Alexander<sup>52, 54</sup> has reported the appearance of a streptomycin resistant strain of *H. influenzae* type b in the nasopharynx as well as in the cerebro-



TABLE II  
Relevant Findings in Cases of Meningitis Due to *Hemophilus influenzae* Treated with Streptomycin at the Boston City Hospital

Case	Age	Previous Therapy	Streptomycin Therapy				Blood Culture Before Streptomycin	Days from First Dose until C.S.F. Cultures Were All Negative	<i>H. influenzae</i>		C.S.F. Levels, Units per Ml.	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course		
			Intra-muscular		Intra-thecal				Type	M.I.C.						
			Day Be- gun	Mg. per Day	Days	Mg. per Day									Days	
1	4 mos.	Penicillin + sulfadiazine, 1 day	4	500	8	50	6	None	Positive	1	b	1.6	3-13	Recovery, complete	yes	"Moribund" on entry; prompt improvement on streptomycin (see figure 1).
2	4 mos.	Penicillin + sulfadiazine, 3 days	6	200	5	30	5	Sulfadiazine	—	0	*	0.8	3-6	Recovery, complete	?	Afebrile 5th day; secondary bout of fever for 11 days, cause not determined.
3	6 mos.	Sulfadiazine + antiserum, 5 days	9	500	14	50	15	Penicillin and sulfadiazine	—	1	b	3.1	3-6	Recovery, complete	0	Prompt improvement only after streptomycin was started.
4	6 mos.	Penicillin + sulfadiazine, 1 day	7	500	2½	50	2	Sulfadiazine 1 day	Positive	1	b	—	3	Died	—	Convulsions for several days before treatment was started; no clinical improvement. No autopsy.
5	7 mos.	Penicillin + sulfadiazine, 1 day	1	1200	3	25	3	None	Negative	0	—	—	—	Recovery, complete	0	Organisms identified at another hospital, seen in smears but cultures negative before streptomycin. Prompt improvement.
6	8 mos.	None	2	800	16	25	8	None	Positive	1	b	1.6	3-10	Recovery, complete	?	Prompt improvement. Afebrile after fifth day of therapy. (Previously reported <sup>37</sup> )
7	9 mos.	Penicillin + sulfadiazine, 1 day	3	800	10	50	10	None	Positive	1	b	3.1	2	Recovery, complete	yes	Marked clinical improvement with subsidence of fever in 6 days.
8	9 mos.	None	6	500 800	4 7	50	12	Penicillin, Sulfadiazine later	Positive	1	b	0.8	6	Recovery; probably deaf and blind	yes	Three bouts of fever; first ended with clinical improvement on 6th day; second ended when streptomycin was stopped; last (cause undetermined) subsided on sulfadiazine therapy.

TABLE II—Continued

Case	Age	Previous Therapy	Streptomycin Therapy				Other Therapy	Blood Culture Before Streptomycin	Days from First Dose until C.S.F. Cultures Were All Negative	<i>H. influenzae</i>		C.S.F. Levels, Units per Ml.	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course
			Day Be- gun	Intra- muscular	Intra- theal	Mg. per Day	Mg. per Day			Type	M.I.C.				
9	11 mos.	Penicillin 1 day, sulfadiazine 4 days	5	500	7	50	6	None	—	1	b	3.1	2-6	0	No effect from other therapy; prompt improvement after streptomycin was given.
10	11 mos.	Penicillin + sulfadiazine + antiserum, 10 days	12	800	6	25	3	None	—	1	b	—	—	0	Relapse after antiserum and during sulfadiazine therapy. Gradual improvement after streptomycin was started. (Previously reported <sup>14</sup> )
11	18 mos.	Penicillin + sulfadiazine, 1 day	3	1000	7	50	7	Sulfadiazine, 2 days	Negative	12 hrs.	b	3.1	2	yes	Rapid improvement, afebrile first time on third day of streptomycin.
12	18 mos.	Penicillin 1 day, sulfadiazine 3 days	1	500	9	50	9	None	Negative	1	b	1.6	2-6	0	Slow improvement, secondary fever with pharyngitis responded to sulfadiazine (figure 2).
13	2 yrs.	Penicillin + sulfadiazine, 1 day	3	1000	8	50	8	Sulfadiazine after 6 days	Positive	1	b	0.4	3-6	0	Improvement and drop in fever over 5 days; secondary fever with otitis responded to sulfadiazine.
14	2 yrs.	Sulfadiazine, 1 day	4	1000	8	50	7	Sulfadiazine after 4 days	—	1	b	1.6	2-6	0	Improved and afebrile third day; otitis and tonsillitis ( <i>Staph. aureus</i> ) later, improved during sulfadiazine therapy.
15	5 yrs.	Penicillin + sulfadiazine, 12 hours	1	1200	6	50	6	None	—	12 hrs.	b	3.1	3-6	yes	Improved and afebrile by fourth day.
16	1 yr.	Penicillin + sulfadiazine, 1 day each	1	2000 1333	2 6	50	5	None	Positive	12 hrs.	b	0.8	—	?	Diffuse macular rash, 6th and 7th days. Also severe local reaction to Schick test 4th to 12th day.

\* Organism did not react with available diagnostic typing sera.

M.I.C. = Minimum inhibiting concentration (complete) of streptomycin in units per ml.<sup>17</sup>

C.S.F. = Cerebrospinal fluid.

— = Not done.

spinal fluid of a child with meningitis during streptomycin therapy. Following recovery by the use of sulfadiazine and specific antiserum the child continued to harbor the resistant organism in the nasopharynx over a period of one year. The epidemiological implications of this observation are obvious.

Alexander<sup>52, 54</sup> has also shown that cultures of *H. influenzae* which have not been previously exposed to streptomycin may contain some organisms which are apparently innately resistant to streptomycin. By inoculating large numbers of organisms into Levinthal agar containing graded dilutions of streptomycin she found organisms resistant to 1000 units per ml., though by ordinary sensitivity studies the strain would appear to be completely inhibited by 1 to 3 units of streptomycin per ml. The incidence of these streptomycin resistant organisms varied from 1 in 1.1 billion to 1 in 13.8 billion organisms. Klein and Kimmelman<sup>55</sup> demonstrated similar findings among strains of *Shigellae*, and Miller<sup>56</sup> in strains of meningococci.

The occurrence of secondary complicating infections during streptomycin therapy of influenzal meningitis by organisms relatively insensitive to streptomycin was described by Weinstein.<sup>44</sup> Three of his nine cases developed complicating staphylococcal infections while receiving streptomycin. One of them died of staphylococcal pneumonia despite penicillin therapy; the second had meningitis and the third otitis media and both of the latter recovered after penicillin was given.

#### CASE REPORTS

At the Boston City Hospital, 16 infants and children with meningitis due to *H. influenzae* have been treated with streptomycin and all but one of them have recovered. The pertinent findings in all of these cases are listed in table 2. The details of the course and treatment in Cases 1 and 12 are shown in figures 1 and 2, respectively. Cases 6 and 10 were included in a previous report.<sup>57</sup>

The ages ranged from four months to five years and 10 of the patients were less than one year old. Blood cultures were done before streptomycin was started in 10 patients and were positive in seven. It was the practice to discontinue other medications when streptomycin was begun though in the severely ill patients this was not always done. In 15 patients there was a satisfactory response to streptomycin with prompt disappearance of the organisms from the cerebrospinal fluid. The clinical response of these patients was fairly rapid, improvement usually occurring during the first 24 to 72 hours of therapy. This improvement was manifested by a return to a normal state of consciousness, cessation of convulsions and irritability and return of the ability to feed properly. The subsidence of the fever was somewhat slower than the other clinical and laboratory evidence of improvement; the temperature did not usually reach normal for a period of four to seven days.

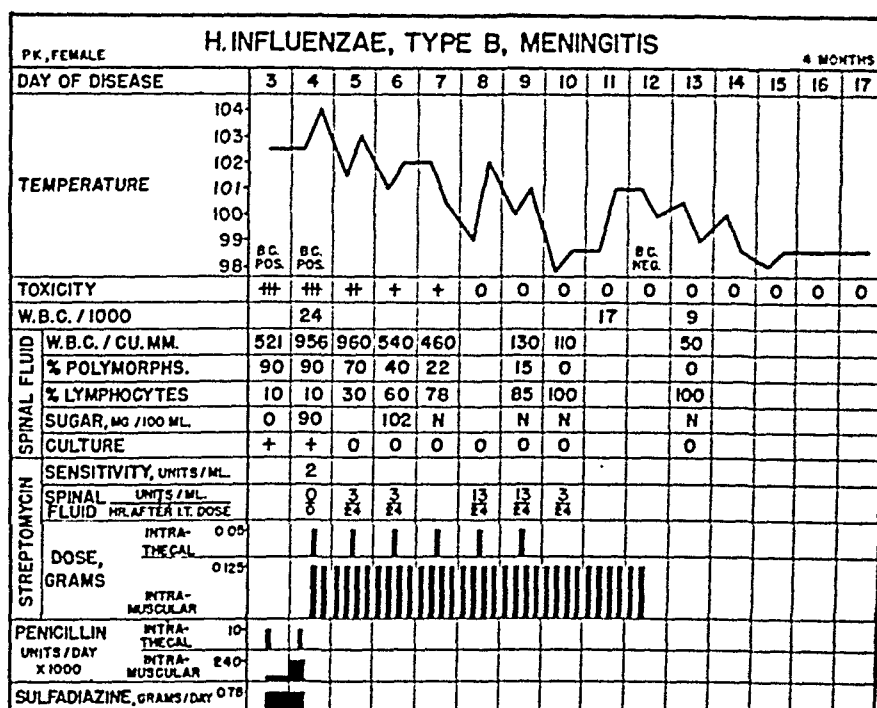


FIG. 1. Case 1. Subsidence of fever by the fifth day of therapy coincided with clinical improvement. A second febrile episode ended after intrathecal streptomycin was discontinued and a third after the intramuscular injections were stopped. Recovery thereafter was uneventful.

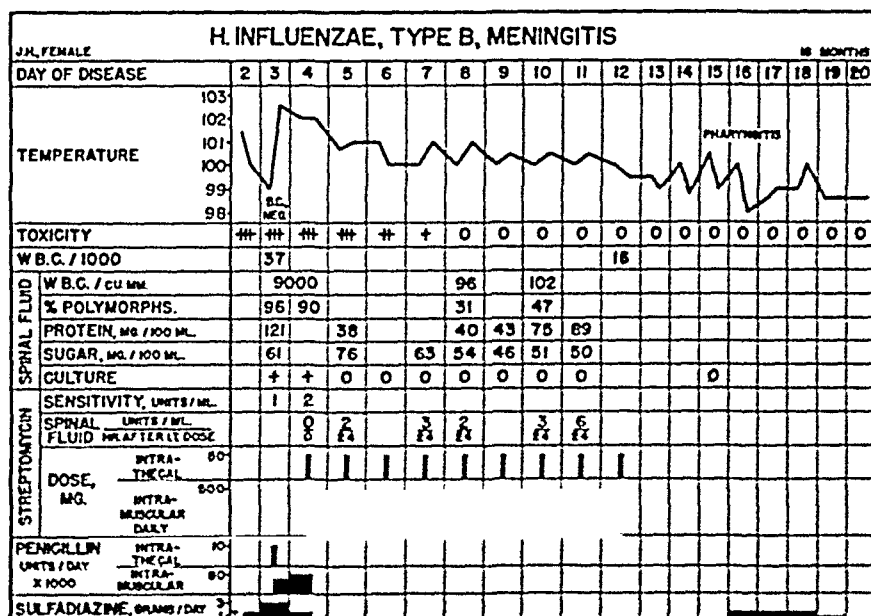


FIG. 2. Case 12. The temperature remained moderately elevated throughout the period of streptomycin therapy and despite prompt and continued clinical improvement. There was also a slight secondary increase in the protein of the cerebrospinal fluid toward the end of therapy. Pharyngitis with fever appeared after streptomycin was stopped and cleared promptly with the use of sulfadiazine. There were no other complications.

The patient who did not respond to streptomycin (Case 4) was a six month old infant who had had convulsive seizures for several days before entering the hospital. Streptomycin was begun on the seventh day of illness and cultures of the cerebrospinal fluid were negative thereafter. There was no clinical improvement, however, and death occurred on the third day of therapy. The cause of death was not determined.

Neurological sequelae were noted only in Case 8. In this nine month old infant treatment was begun on the sixth day of the disease and following recovery the patient was deaf and blind.

The appearance of resistant strains of *H. influenzae* was not demonstrated in this series. It is not possible, however, to rule out the presence of such resistant organisms in some localized areas of infection in the fatal case even though the cerebrospinal fluid cultures were negative before death.

Complicating infections, notably acute pharyngitis and otitis, occurred during or after the course of streptomycin therapy in four patients and possibly in a fifth. It was not always possible to identify the causative organisms in these infections. The institution of sulfadiazine, however, was followed by subsidence of fever and symptoms in each instance.

The occurrence of secondary fever after an initial response to therapy suggests one of at least four possibilities: (1) a relapse of the original infection, (2) focal purulent complications such as a brain abscess, (3) a secondary complicating infection by another organism or (4) drug fever. Obviously, the proper interpretation of the secondary fever is very important. In the present series, secondary fever, apparently related to the streptomycin, appeared in five patients and possibly in three others. In these cases the secondary fever subsided promptly after the streptomycin was stopped.

The course of the cases with streptomycin fever is of interest. The initial fall in temperature occurred between the fourth and seventh day of therapy and was accompanied by clinical and laboratory evidence of improvement. A secondary rise in temperature occurred shortly thereafter and continued as long as the streptomycin was given. The clinical and laboratory evidence of improvement continued in these cases in spite of this fever. In most of the patients both the intramuscular and the intrathecal injections were stopped at about the same time. In Case 1, however, there were two febrile episodes, the first subsiding when the intrathecal injections were stopped and the second only after the intramuscular injections were discontinued. The course in this case is shown in figure 1.

#### MENINGITIS DUE TO OTHER GRAM-NEGATIVE BACILLI

Infections of the central nervous system by gram-negative bacilli other than *Hemophilus influenzae* are infrequent. The coliform organisms are the ones most often implicated.<sup>58</sup> The incidence of meningitis due to coliform bacteria is highest in infants under three months,<sup>1, 7, 11, 59</sup> suggesting a

low degree of resistance to such infections in this age group.<sup>55, 60</sup> The other gram-negative bacilli which are less often encountered as the cause of meningitis may occur in any age group, and comprise a wide variety of organisms including *Alkaligenes fecalis*,<sup>53</sup> *Acrobacter aerogenes*,<sup>55</sup> *Klebsiella pneumoniae*,<sup>1, 61, 62</sup> *Pasteurella tularensis*,<sup>63</sup> *Proteus morgani* and *Proteus vulgaris*,<sup>53, 64, 65</sup> *Pseudomonas aeruginosa*,<sup>66</sup> the salmonella group,<sup>1, 67</sup> *Serratia marcescens*<sup>68</sup> and others.

Meningitis caused by these organisms usually occurs by direct extension from an adjacent focus of infection in the paranasal sinuses, ear, mastoid, a brain abscess or a meningocele. It may follow skull fractures or contaminated lumbar puncture or spinal anesthesia procedures.<sup>12, 57, 58, 64, 66, 69</sup> It may also arise by hematogenous spread from a distant focus of infection; cases of coliform meningitis in infants seem to arise largely in this manner.<sup>7, 11, 58</sup>

The use of sulfonamides has resulted in some lessening of the mortality in this type of meningitis but such infections are still quite serious and penicillin apparently has little to offer.<sup>57, 63, 66, 67, 70-72</sup> The outcome in some of these cases may also depend on successful surgical drainage of purulent foci of suppuration.\*

Several authors have reported on the use of streptomycin in meningitis due to this group of gram-negative bacilli. The pertinent findings in their cases are listed in table 3. Though the over-all mortality in this group of cases is high (45 per cent), it is probable that in many of these patients as in those of influenzal meningitis, treatment with streptomycin was begun late and only after therapy with other agents had failed.

Streptomycin has been shown to be active in vitro against most of these gram-negative bacilli and it is effective in experimental infections of animals with some of them.<sup>40</sup> The early institution of intramuscular and intrathecal streptomycin when combined with surgery wherever indicated should, therefore, go far towards lowering the mortality rates in meningitis due to these organisms. Inasmuch as systemic infections with *Brucella* and *Salmonella*, including typhoid fever, have not responded favorably to streptomycin, its effects in meningitis due to these organisms cannot be predicted. Streptomycin should, nevertheless, receive a trial in these infections.

\* A recent report<sup>101</sup> records 12 fatal cases of meningitis following penetrating wounds of the cranium and the spinal canal. Seven of the deaths were attributable to *Klebsiellae*, three to *Acrobacter aerogenes* and one each to *B. coli* and a *Shigella*. Four additional patients with superficial infections of the brain with *K. pneumoniae* not involving the ventricles survived in 10 of these 16 cases including all of the survivors, there was a mixed infection with gram-positive organisms. All were treated intensively with sulfonamides and penicillin and one who recovered was also given chloral hydrate intrathecally.

Another recent case<sup>102</sup> of interest is that of a month old infant in whom an *A. aerogenes* meningitis and septicemia cleared completely following treatment with penicillin and sulfathiazole. The infant subsequently died of an underlying bilateral hydronephrosis and pyelonephritis shortly after treatment with streptomycin was started. The latter infection was due to *E. coli* and no evidence of the meningitis was found at autopsy.

TABLE III  
Meningitis Due to Gram-Negative Bacilli Other Than *Hemophilus influenzae*  
Summary of Reported Results in Streptomycin-Treated Cases

Author	Num-ber of Cases	Organism	Previous Treatment	Concomitant Treatment	Streptomycin*				Result		Remarks
					Intra-muscular		Intra-theal		Re-cov-ered	Died	
					Mg. per Day	Days	Mg. per Day	Days			
DeBakey and Pulaski <sup>13</sup>	1	<i>A. aerogenes</i>	—	—	—	—	—	—	1	Adult. Infection followed laminectomy. Moribund when treatment was begun. Died 9½ hours after first dose.	
Edwards and Kirk <sup>74</sup>	1	<i>A. cloacae</i>	Streptomycin, intramuscular	—	1000-1500	36	0	0	—	1	Adult. Meningitis developed during intramuscular streptomycin therapy for osteomyelitis of ilium with bacteremia. Organism became resistant to streptomycin.
Cairns et al. <sup>45</sup>	1	An achromobacterium	—	Penicillin, sulfonamides	0	—	80	2	1	—	Organisms not found after first injection of streptomycin.
N.R.C. <sup>53</sup>	4	<i>Alk. fecalis</i>	*	*	500	9	100	6	4	—	Three of these patients listed as "improved."
Alexander <sup>75</sup>	1	<i>E. coli</i>	Penicillin	None	1600 1000	4 12	50	13	1	—	Adult. Infection followed spinal anesthesia for reamputation of foot. No organisms found after 4th day of treatment.
N.R.C. <sup>53</sup>	3	<i>E. coli</i>	*	*	500	9	100	6	3	—	Two of these patients listed as "improved."
Zantiny and Carlson <sup>17</sup>	1	<i>E. coli</i>	None	None	800	12	0	0	1	—	23-day old infant. Infection followed operation on congenital meningocoele, C.S.F. cultures negative 48 hours after streptomycin was begun.
Shields <sup>76</sup>	1	<i>E. coli</i>	Penicillin and sulfadiazine	None	240	10	30	10	1	—	5-week old infant. Cultures of C.S.F. negative after 2d day of treatment. No sequelae.
DeBakey and Pulaski <sup>13</sup>	1	<i>E. coli</i>	—	—	—	—	—	—	1	—	—
N.R.C. <sup>53</sup>	2	<i>K. pneumoniae</i>	*	—	500	9	100	6	—	2	—
Tartakoff et al. <sup>82</sup>	1	<i>K. pneumoniae</i>	Penicillin and sulfadiazine	—	3000	3	50 intracisternal	3	—	1	Adult. Meningitis followed craniotomy. Culture of C.S.F. negative on 7th day of disease when streptomycin was started.
Hough and Adelson <sup>102</sup>	1	<i>K. pneumoniae</i>	—	Penicillin and sulfathiazole	150	7	50	1	—	1	29 years old. Post abortive septicemia and meningitis. <i>K. pneumoniae</i> , type B, cultured from blood, cerebrospinal fluid and uterus at autopsy.

TABLE III—Continued

Author	Num-ber of Cases	Organism	Previous Treatment	Concomitant Treatment	Streptomycin*				Result		Remarks
					Intra-mus-cular		Intra-the-cal		Re-cov-ered	Died	
					Mg. per Day	Days	Mg. per Day	Days			
N.R.C. <sup>11</sup>	1	<i>P. morgani</i>	*	*	500	9	100	6	1		
N.R.C. <sup>11</sup>	2	<i>P. vulgaris</i>	*	*	500	9	100	6	1	1	
DeBakey and Pulaski <sup>12</sup>	1	<i>P. vulgaris</i>	—	—	—	—	—	—	1		
N.R.C. <sup>11</sup>	2	<i>S. salmonella</i>	*	*	—	—	—	—	1	1	
Burns <sup>13</sup>	1	<i>S. cholerae sus</i>	Penicillin and sulfamerazine	—	60	6	100	6		1	Newborn. Streptomycin begun on 20th day of disease. Improved clinically, but C.S.F. cultures remained positive.
MacFarlane <sup>14</sup>	1	<i>S. schottmulleri</i>	Penicillin and sulfadiazine	Sulfadiazine	100	11	0	intracerebral	1		Newborn. Treatment begun late. C.S.F. cultures became negative. Died about 1 month later of hydrocephalus.
Cutler et al. <sup>15</sup>	3	<i>Ps. aeruginosa</i>	Penicillin and sulfonamides	—	0		(1) 80 (2) 50 (3) 100	13 4 2		3	Streptomycin given intraventricularly to 2 patients. All very ill at start of treatment.
DeBakey and Pulaski <sup>12</sup>	1	<i>Ps. aeruginosa</i>	—	—	—	—	—	—	1		17 years old. <i>B. pyocyaneus</i> sepsis complicating disseminated lupus treated with streptomycin subcutaneously. Meningitis developed during streptomycin therapy.
Stanley <sup>16</sup>	1	<i>Ps. aeruginosa</i>	Penicillin, streptomycin and sulfadiazine	Sulfadiazine	2000	5	0			1	
Merritt et al. <sup>17</sup>	1	<i>Ps. aeruginosa</i>	Penicillin and sulfadiazine	Sulfadiazine 7 days	1000	15	50-100	15	1		23 years old. Meningitis followed spinal anesthesia. Vertigo during treatment. Flaccid paraplegia developed 3 weeks later and was attributed to neurotoxic reaction to streptomycin.
Morgan and Hunt <sup>18</sup>	1	Gram-negative bacillus unidentified	—	—	—	—	—	—		1	Meningitis followed craniotomy. Intrathecal and intramuscular streptomycin resulted in fall in temperature and disappearance of organism from C.S.F. Spinal block developed and patient died. Organism cultured from cerebellar abscess at autopsy resistant to 1000 units; pretreatment strain inhibited by 2 units.
Totals	11								18	15	

\* Data not given.

<sup>11</sup> Most of the patients included from the N.R.C. report received penicillin and sulfonamides before and some also during streptomycin therapy. The streptomycin doses in these cases are averages.

<sup>12</sup> DeBakey and Pulaski's cases have been reported in greater detail by Pulaski and Matthews<sup>19</sup> who added 2 cases, 1 due to *E. coli* and the other to *K. pneumoniae*; both recovered after treatment with streptomycin, penicillin and sulfadiazine.



Cases of Meningitis Due to Organisms Other Than *Hemophilus influenzae* That Were Treated with Streptomycin at the Boston City Hospital

Case	Age	Previous Therapy	Organism	M.I.C., Units per Ml.	Streptomycin Therapy					C.S.F. Levels, Units per Ml.*	Other Therapy	Days from First Dose until C.S.F. Cultures Were All Negative	Outcome	Secondary Fever Attributable to Streptomycin	Remarks on Clinical Course
					Day Be- gun	Intra- muscular		Intra- thecal							
						Mg. per Day	Days	Mg. per Day	Days						
17	38 yrs.	Penicillin, 4 days, sulfadiazine, 20 days	<i>Aerobacter aerogenes</i>	13	20	4000	10	200-50	10	None	1	Recovered	yes		Details shown in figure 3.
18	2 mos.	Penicillin, 14 days	<i>Escherichia coli communis</i>	6	?	500	1	50	1	Sulfadiazine	Cultures remained positive	Died	—		Moribund with positive blood culture before treatment and after severe intractable diarrhea (etiology unknown). Died after 2 injections. C.S.F. cultures remained positive and organism remained sensitive.
19	57 yrs.	Penicillin + sulfadiazine, 2 days	<i>Hemophilus para-influenzae</i>	6	3	4000	10	100 50	3 5	Penicillin + sulfadiazine	1	Recovered; ataxia	yes?		Followed skull fracture. Loss of vestibular reflexes began on tenth day and was complete; postural compensation was almost complete in 3 weeks.
20	20 yrs.	Penicillin + sulfadiazine, 19 days	"Pleuro-pneumonia"	25	19	4000	7	50	10	Penicillin + sulfadiazine	11	Recovered	0		Brain abscess and meningitis after stem of "smoking" pipe was thrust through orbit. Marked clinical improvement coincided with start of streptomycin. Details to be reported elsewhere.
21	4 mos.	Penicillin, 6 days, sulfadiazine, 2 days	<i>Proteus morgani</i>	50	6	400	10	50	7	None	1	Recovered	yes		Followed operation on meningococci. No complications. (Case 3 in reference 57.)
22	11 days	Penicillin, 4 days	<i>Pseudomonas aeruginosa</i>	50	4	200	36	25-50	15	None	27	Recovered; rt. facial paralysis	yes		Followed surgical debridement of infected meningococci. Clinical improvement before cultures were negative. (Case 2 in reference 57.)
23	12 days	Penicillin, 2 days	<i>Pseudomonas aeruginosa</i>	25	3	200	23	10 25	13 10	Penicillin intramuscularly	Cultures remained positive	Died	0		Details of the course and therapy are shown in figure 4.
24	14 yrs.	Penicillin + sulfadiazine, 3 days	<i>Pseudomonas aeruginosa</i>	13-50	4	4000	7	50	8	Sulfadiazine	4	Recovered	yes		Meningitis followed lumbar puncture. No complications. (Case 1 in reference 57.)

\* 24 hours after previous intrathecal injection except in Case 17 in which most of the levels were obtained after 12 hours.

## CASE REPORTS

At this hospital eight patients with meningitis due to gram-negative bacilli, other than *H. influenzae*, have been treated with streptomycin and six of them have recovered. There were three patients with meningitis due to *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), and one patient each with meningitis due to *Proteus morgani*, *Aerobacter aerogenes*, *Escherichia coli communis*, *Hemophilus parainfluenzae* and a "pleuropneumonia-like" organism. Some of the relevant details of these cases are listed in table 4, and the clinical and laboratory findings in Cases 17 and 23 are shown in figures 3 and 4, respectively. Three of the cases have been reported previously.<sup>57</sup>

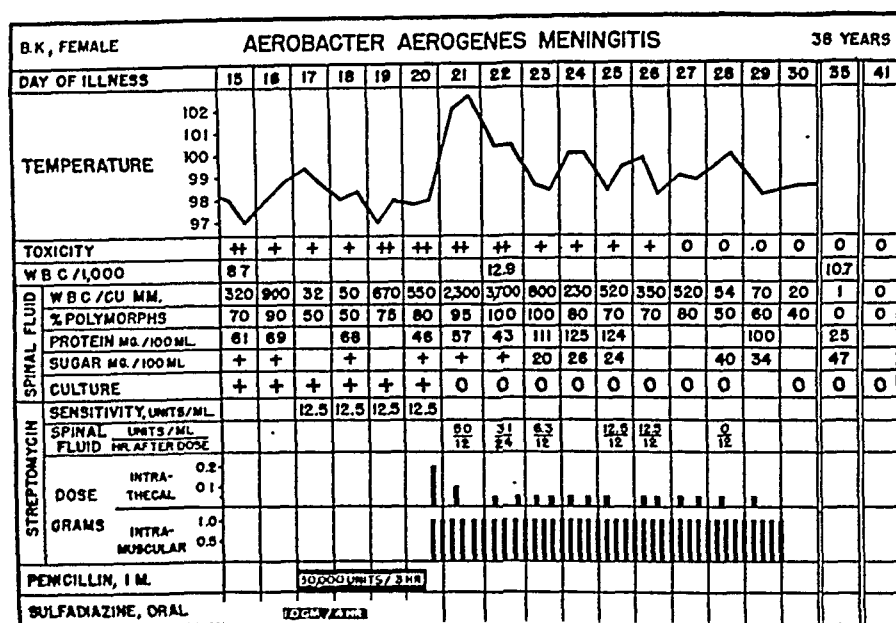


FIG. 3. Relevant findings in Case 17. The meningitis began while the patient was receiving sulfadiazine prophylactically for a skull fracture and persisted after intramuscular and intrathecal penicillin was added to the treatment. (The latter is not shown in the chart.) Cultures of the cerebrospinal fluid became negative after the first intrathecal dose of streptomycin and remained so. There was a sharp febrile reaction, with increase in signs of meningeal irritation and also in the cellular and protein content of the cerebrospinal fluid after the initial intrathecal injection of 200 mg. of streptomycin. The increased pleocytosis continued when 100 mg. were given but the reaction subsided when the intrathecal doses were reduced to 50 mg. each. Recovery was uneventful.

The pathogenesis of these cases is of interest. In three patients the meningitis was secondary to trauma to the head; in three others it was secondary to infection of a congenital meningocele; one case followed a diagnostic lumbar puncture and in another the meningitis was associated with a bacteremia.

Penicillin with or without sulfadiazine had been given to all of these patients without effect before the institution of streptomycin. Moreover, in Case 18 the meningitis developed during penicillin treatment for diarrhea

and in Case 19 it began during prophylactic administration of sulfadiazine and penicillin following a fracture of the skull. One or both of these agents was also given during the streptomycin administration in five of the patients.

There were two deaths in this group of eight patients. One of these deaths was in a 12-day old infant and followed the development of streptomycin resistance by the infecting organism (Case 23, see figure 4). The other (Case 18) occurred after only 12 hours of treatment in an infant who was moribund when the streptomycin was started.

There was evidence of clinical improvement shortly after streptomycin was begun in all of the patients who recovered. In three of them, however, organisms persisted in the cerebrospinal fluid for a varying number of days

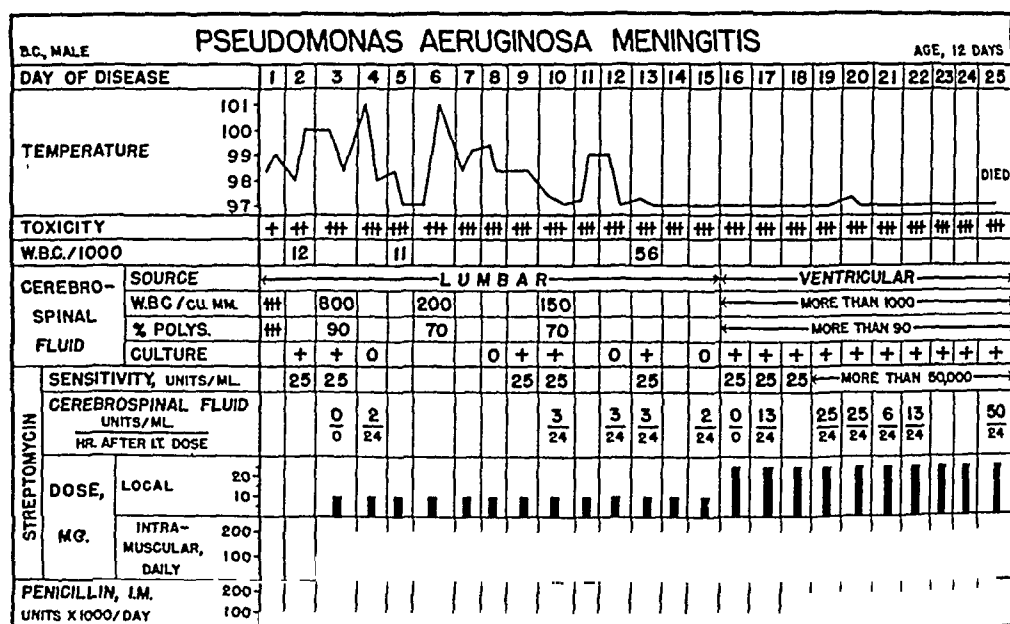


FIG. 4. Course and relevant findings in Case 23. The meningitis followed erosion and infection of a congenital meningocele. There was no clinical improvement on streptomycin and the course was steadily downward in spite of subsidence of fever. Cultures of the cerebrospinal fluid remained positive. Injections were given into the lateral cerebral ventricles through the anterior fontanelle after a block developed. There were frequent convulsions before that time but not thereafter. The organisms obtained after the sixteenth day of treatment were all completely resistant to streptomycin.

during streptomycin treatment. Secondary fever attributable to streptomycin occurred in four and possibly a fifth patient; in these cases, as in those due to *H. influenzae*, clinical and laboratory evidence of improvement continued during the secondary febrile episode. There were no complicating infections with other organisms in any of these cases. The only residual neurologic damage among those who recovered was a right facial palsy in Case 22. As already noted, a resistant strain appeared during treatment in one patient, Case 23, and that patient died. In another patient, Case 20, the organism was recovered from the cerebrospinal fluid throughout the

period of treatment; the organism retained its original sensitivity for six days and was resistant during the last four days. The organism then disappeared from the spinal fluid and the patient recovered.

### TUBERCULOUS MENINGITIS

The frequency with which *Mycobacterium tuberculosis* involves the meninges may be noted in table 1. Infants and children are affected more often than adults. Tuberculous meningitis probably arises in most cases by hematogenous spread from a focus of infection elsewhere in the body though in some cases it occurs by direct extension from a tuberculous lesion of the brain. Prior to the use of streptomycin tuberculous meningitis was a uniformly fatal disease.

Streptomycin was early shown to be effective against *M. tuberculosis* in vitro,<sup>79</sup> and in experimental infections in animals.<sup>80</sup> The in vitro sensitivity of a large number of strains of *M. tuberculosis* isolated from cases of human infection was found to be less than 1 unit per ml.<sup>79, 81-83</sup>

Reports are now available in 32 cases of tuberculous meningitis that have been treated with streptomycin.<sup>65, 81-91</sup> At the time when they were reported, 13 of this group of patients were still living. The incidence of permanent neurologic damage was high, however, and the survivors had been followed for only short periods after cessation of streptomycin therapy. The remarkable fact was that they were alive and that their disease was apparently arrested. Histopathological findings in fatal cases have also given evidence of the effectiveness of streptomycin in such cases.<sup>92</sup>

Of considerable interest is the fact that parenteral therapy alone has proved inadequate in these cases. Two patients were noted to develop signs of meningitis during intramuscular streptomycin therapy for miliary tuberculosis and the meningitis apparently responded only after streptomycin was also given intrathecally.<sup>53</sup> The four survivors among the seven patients treated by Hinshaw and his co-workers<sup>90</sup> all received both intramuscular and intrathecal therapy while the fatal cases received the drug only intramuscularly. A prolonged period of combined parenteral and intrathecal streptomycin seems indicated in this condition.<sup>90</sup>

The appearance of streptomycin resistant strains of *M. tuberculosis* has not been reported as occurring specifically during therapy of tuberculous meningitis but resistant strains have appeared frequently in patients with pulmonary tuberculosis while on streptomycin therapy.<sup>90, 93, 94</sup> There is no reason to believe that similar resistant strains will not also be noted during the streptomycin treatment of meningeal tuberculosis.

### CASE REPORTS

Three patients with tuberculous meningitis have been treated with streptomycin at the Boston City Hospital. In each instance the diagnosis was proved by guinea pig inoculation of cerebrospinal fluid obtained just prior

to institution of therapy. Streptomycin was given intrathecally and intramuscularly to all three patients. There was one death in this group. A brief description of the three cases follows:

*Case 25.* Treatment was begun in this seven year old child approximately 10 days after the onset of symptoms. Streptomycin was given intramuscularly, 0.5 gm. daily in divided doses, for 142 days. It was also given intrathecally throughout this period—25 mg. daily for the first 45 days, and 50 mg. every other day for the next 20 days and twice weekly thereafter. There was progressive improvement in the clinical condition of the patient over a period of about a month. During the daily intrathecal injections of streptomycin, however, there was a gradual rise in the protein content of the cerebrospinal fluid and it fell again only when the injections were given at longer intervals. Tubercle bacilli were recovered from the cerebrospinal fluid by guinea pig inoculation before streptomycin was started and again after four days of therapy, but thereafter all guinea pig inoculations were negative. There was slight residual weakness in the left arm and the left leg at the conclusion of treatment but there were no other neurologic defects and psychiatric examination revealed no evidence of mental impairment. When examined two months after the streptomycin was stopped the patient was continuing to improve.

*Case 26.* Streptomycin was started in this 10 month old infant one week after the onset of symptoms and has been continued over a period of  $3\frac{1}{2}$  months. The dosage used was 125 mg. intramuscularly every six hours and intrathecal injections of 50 mg. each given daily for 40 days and twice a week thereafter. The intrathecal injections were given first by the lumbar route and later into the lateral cerebral ventricles through the anterior fontanelle. There were occasional convulsions during the period of daily intraventricular injections but these subsided when the injections were given twice a week. The cerebrospinal fluid protein has remained elevated in this case. The infant has improved clinically and the temperature has gradually returned to normal. At the present time the infant seems blind but there is no other obvious neurologic damage. Guinea pig inoculations of the cerebrospinal fluid were positive before the streptomycin was started and have been negative since then.

*Case 27.* This  $2\frac{1}{2}$  year old child had symptoms for approximately two weeks before treatment was begun. Streptomycin was given in doses of 250 mg. every six hours and 50 mg. intrathecally once each day for 17 days. There was no apparent clinical improvement and the patient died. There was no autopsy.

The ideal drug for the treatment of tuberculosis is not yet at hand. Streptomycin is undoubtedly the best one available at present but it has many shortcomings, particularly the ease with which organisms may become resistant to it. A trial of the simultaneous use of streptomycin with one of the sulfone drugs such as Promin, Diasone or Promizole, in the treatment of tuberculosis certainly seems indicated since such a combination appears to be more effective than the use of either alone in experimental infections in animals.<sup>95, 96</sup>

#### UNTOWARD REACTIONS

Fever was the most frequent untoward reaction from streptomycin noted in the patients treated for meningitis at the Boston City Hospital. A secondary febrile episode attributable to the streptomycin occurred in nine patients, and possibly in four others, among the 24 nontuberculous cases. Such a

reaction was more difficult to interpret in those with tuberculous meningitis. In some of the cases the secondary fever may have been related chiefly to the intrathecal injections since the fever subsided promptly when those injections were discontinued. Furthermore, the fever in some of them was associated with a secondary increase in the cellular and protein content of the cerebrospinal fluid. In one patient the fever again recurred following the discontinuance of intrathecal therapy and persisted until the intramuscular injections were stopped.

An increase in the protein content of the cerebrospinal fluid not associated with an increase in the number of cells was noted in two patients with tuberculous meningitis while they were receiving daily intrathecal injections over a long period. The protein level slowly fell when the intrathecal injections were spaced at longer intervals.

The largest single intrathecal dose of streptomycin was 200 mg. given initially in Case 23. Shortly after this injection, the patient exhibited transient irritability and some clonic movements of the lower extremities and this was followed by a marked rise in temperature. Cerebrospinal fluid removed 24 hours after this injection showed a marked increase in the number of leukocytes, mostly polymorphonuclears, and there was also a moderate increase in protein. The cerebrospinal fluid findings gradually returned toward normal when the size of the intrathecal dose was decreased.

Ataxia was observed only in Case 19. It was first noted on the tenth day of streptomycin therapy. Caloric and rotation tests showed complete absence of vestibular response in this case but the patient was gradually able to compensate for this defect. There was some loss of hearing at this time but its relation to the therapy could not be evaluated.

One patient (Case 16) developed a macular, erythematous rash on the sixth day of streptomycin therapy. The rash cleared in about 48 hours coincident with discontinuance of the streptomycin. There were no other reactions referable to other organs in any of the patients.

### DISCUSSION

The findings in the present cases indicate that streptomycin is of considerable value in the treatment of meningitis due to gram-negative bacilli. The drug should be given both intramuscularly and intrathecally. In adults an intramuscular dose of 1 gm. every six hours and a single daily intrathecal injection of 50 mg. appears to be adequate for most cases. Somewhat larger doses, 1 gm. every four hours intramuscularly and 50 to 100 mg. intrathecally twice a day for one or two days, may be given but are probably not necessary in most cases. Infants and small children may be given about 25 mg., or slightly more, per pound of body weight per day intramuscularly and 10 to 50 mg. daily by the intrathecal route.

Most cases of meningitis due to gram-negative bacilli seem to respond well to streptomycin alone if the treatment is started early in the course of

the disease. If treatment is begun late, however, or if the patient is severely ill when the treatment is started, sulfadiazine should probably be given in addition. Likewise, in cases due to *H. influenzae* type b, specific antiserum and sulfadiazine should also be given under similar circumstances. The possibility of inhibiting the development of streptomycin resistant strains by the combined use of sulfadiazine and streptomycin has been suggested.<sup>97</sup> Penicillin should also be used whenever an infection with a susceptible organism is present or suspected. The possible use of large doses of penicillin specifically for their effect on certain gram-negative bacillus infections warrants further exploration.

In tuberculous meningitis, the early and persistent use of streptomycin may offer the only hope of arresting the disease. It is essential that cerebrospinal fluid be obtained for culture or guinea pig inoculation, or both *before* streptomycin is started since these procedures may later yield negative results and leave the diagnosis in doubt. The streptomycin should be given in these cases both intramuscularly and intrathecally over a period of three or possibly four months. The doses required in cases of tuberculous meningitis may be somewhat smaller than those used in infections with gram-negative bacilli due to the greater sensitivity of the strains of *M. tuberculosis*. The intrathecal doses should be given daily for three to five weeks and at gradually increasing intervals up to twice weekly thereafter.

Excessively large individual doses by intrathecal injection should be avoided in all cases. They are known to produce serious reactions in animals<sup>98</sup> and in humans.<sup>45, 99</sup> It appears likely that the concentration of streptomycin in the solution injected as well as the total amount may be an important factor in these reactions as has been suggested in the case of penicillin.<sup>100</sup>

### SUMMARY AND CONCLUSIONS

Streptomycin has been used in the treatment of 27 cases of meningitis at the Boston City Hospital. There was one death among 16 cases due to *Hemophilus influenzae* and two deaths among eight cases due to other gram-negative bacilli. The deaths occurred in two patients in whom treatment with streptomycin was begun late in the disease and in the third it was associated with the development of a streptomycin resistant strain of *Pseudomonas aeruginosa* during treatment. Two of three patients with tuberculous meningitis are living and their disease appears to be arrested.

The results in these cases and in similar cases reported by others seem to justify the following conclusions:

1. Streptomycin is the only agent now available which may arrest the progress of tuberculous meningitis.

2. Streptomycin is the most effective single agent in the treatment of meningitis due to gram-negative bacilli, including *Hemophilus influenzae*.

*Addendum.* The following is a summary of eight cases of meningitis treated with streptomycin since this paper was submitted.

1. A case of *H. influenzae*, type b meningitis in an infant one year old was treated with streptomycin, 50 mg. intrathecally once a day and 200 mg. intramuscularly every six hours for a total of seven days. The organism was sensitive to 3.1 units. Sulfadiazine was also given during this time. The patient responded promptly and recovered without complications.

2. In a second case of *H. influenzae*, type b meningitis in a 15-month old girl, cultures of the cerebrospinal fluid were still positive after two days of treatment with sulfadiazine. Streptomycin was given as in the previous case. A single dose of specific antiserum was also given 24 hours after the streptomycin was started but the temperature had already dropped and smears and cultures of the cerebrospinal fluid were already negative at that time. The organism was sensitive to 3.1 units. Recovery was rapid, complete and uncomplicated.

3. A case of *E. coli communis* meningitis in a five day old infant with an infected lumbar meningocele was treated with streptomycin for a total of 20 days in doses of 60 mg. every six hours intramuscularly, and 25 mg. were injected daily into alternate cerebral ventricles through the anterior fontanelle. The latter dose was reduced to 10 mg. after 14 days because of persistently high protein levels in the cerebrospinal fluid. Cultures of the cerebrospinal fluid were positive before streptomycin was started in spite of previous penicillin and sulfadiazine therapy, but subsequent cultures were all negative. The organism was inhibited by 12.5 units of streptomycin. Surgical repair of the meningocele was done on the tenth day and a catheter left in the ventricle for 10 days. The infant has apparently recovered without sequelae demonstrable at this time.

4. A case of *E. coli communior* meningitis of unknown duration and pathogenesis in a 68 year old woman was treated with daily doses of 50 mg. of streptomycin intrathecally and 1 gm. every four hours intramuscularly. This was supplemented by sulfadiazine and large doses of penicillin. Cultures of blood and spinal fluid were positive before and after treatment and the patient died on the fifth day. The organism obtained before the first day of streptomycin was completely inhibited by 12.5 units of streptomycin per ml. but those obtained from blood and spinal fluid 24 hours later and all subsequent ones grew uninhibited in a concentration of 50,000 units per ml.

5. A case of *K. pneumoniae*, type A meningitis of otitic origin in a woman 70 years old, was treated with streptomycin 1 gm. every four hours intramuscularly and three intrathecal doses of 50 mg. each at 12-hour intervals. The patient also received sulfadiazine orally and penicillin intramuscularly and intrathecally. The organism was obtained from cultures of cerebrospinal fluid, blood and aural discharge before treatment and was inhibited by 1.56 units of streptomycin per ml. Spinal fluid cultures were still positive 12 and 24 hours after streptomycin was started and the patient died 33 hours after the first dose.

6. An 18-month old girl with tuberculous meningitis and miliary tuberculosis, the former proved by guinea pig inoculation of spinal fluid, was given streptomycin over a period of 3½ months. Intramuscular injections of 250 mg. were given every six hours throughout this period and intrathecal injections of 25 mg. each were given daily for two weeks, then every other day for four weeks and twice weekly thereafter. There was rapid clinical improvement, the pulmonary and meningeal signs cleared and the patient was discharged at the end of the course of treatment apparently cured and without sequelae.

7. A one-year old infant with very similar findings and treated in the same manner died at the end of the fourth week without showing any definite evidence of improvement.



8. A girl 13 years old with tuberculous meningitis and miliary tuberculosis has now been under treatment for six weeks. She had had proved tuberculous arthritis for one year and symptoms of meningitis for one week before the streptomycin was started. She has received 250 mg. intramuscularly every six hours throughout and intrathecal injections of 50 mg. daily for two weeks and every other day thereafter. Clinical improvement was rapid and the patient has been free of fever and symptoms since the first week of therapy.

#### BIBLIOGRAPHY

1. NEAL, J. B.: Diagnosis and treatment of meningitis, *Med. Clin. North Am.*, 1935, xix, 751.
2. TRIPOLI, C. J.: Bacterial meningitis. A comparative study of various therapeutic measures, *Jr. Am. Med. Assoc.*, 1936, cvi, 171.
3. RHOADS, P. S., et al.: Treatment of pneumococcic meningitis, *Jr. Am. Med. Assoc.*, 1940, cxv, 917.
4. FERGUSON, F., and BARR, D.: Glycosuria in meningitis, *Ann. Int. Med.*, 1944, xxi, 173.
5. RHOADS, P. S.: The clinical analysis of 550 cases of bacterial meningitis. Diagnostic features and various methods of treatment, *Am. Pract.*, 1947, i, 305.
6. BRAINERD, H., and BRADLEY, E.: Treatment of bacterial meningitis with penicillin, sulfonamides and sera, *California Med.*, 1947, lxvi, 57.
7. FOTHERGILL, L. D., and SWEET, L. K.: Meningitis in infants and children with special reference to age-incidence and bacteriologic diagnosis, *Jr. Pediat.*, 1933, ii, 696.
8. LINDSAY, J. W., RICE, E. C., and SELINGER, M. A.: The treatment of meningitis due to *Hemophilus influenzae* (Pfeiffer's bacillus). A review of 108 cases, *Jr. Pediat.*, 1940, xvii, 220.
9. SILVERTHORNE, N.: Meningitis in childhood, *Canad. Med. Assoc. Jr.*, 1943, xlviii, 218.
10. KEEFER, C. S.: The treatment of bacterial meningitis, *Med. Clin. North Am.*, 1941, xxv, 1287.
11. HERTZOG, A. J.: A study of 377 cases of fatal meningitis with special reference to bacteriologic diagnosis, *Am. Jr. Clin. Path.*, 1945, xv, 571.
12. POTE, W. W. H., and COURVILLE, C. B.: Intracranial complications of infections of the nasal air passages and accessory sinuses. A further report on the nature and incidence of lesions observed in a series of 30,000 autopsies, *Bull. Los Angeles Neurol. Soc.*, 1945, x, 114.
13. GOOD, P. G., et al.: A study of the familial spread of *H. influenzae*, type b, *Yale Jr. Biol. and Med.*, 1943, xv, 915.
14. STILLMAN, E. G.: Occurrence of *H. influenzae* in throats of adults, *Yale Jr. Biol. and Med.*, 1945, xviii, 37.
15. DAVIS, H. V.: Obstructive laryngitis in children caused by *Hemophilus influenzae* bacillus type b, *Jr. Kansas Med. Soc.*, 1947, xlviii, 105.
16. DOCHEZ, A. R., MILLS, K. C., and KNEELAND, Y., JR.: Variation of *H. influenzae* during acute respiratory infection in the chimpanzee, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxx, 314.
17. PITTMAN, M.: Variation and type specificity in bacterial species *Hemophilus influenzae*, *Jr. Exper. Med.*, 1931, liii, 471.
18. MULDER, J.: *Haemophilus influenzae* of the respiratory type as a cause of purulent meningitis, *Jr. Path. and Bact.*, 1939, xlviii, 175.
19. PITTMAN, M.: A type d strain of *Hemophilus influenzae* previously designated provisionally as type d<sub>2</sub> and type g, *Jr. Bact.*, 1947, liii, 499.
20. PITTMAN, M.: Action of type-specific *Hemophilus influenzae* antiserum, *Jr. Exper. Med.*, 1933, lviii, 683.
21. ALEXANDER, H. E.: Type "B" anti-influenzal rabbit serum for therapeutic purposes, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 313.

22. FOTHERGILL, L. D., and WRIGHT, I.: Influenzal meningitis: Relation of incidence to bactericidal power of blood against causal organism, *Jr. Immunol.*, 1933, xxiv, 273.
23. NEAL, J. B., JACKSON, H. W., and APPELBAUM, E.: A comprehensive study of meningitis secondary to otitis or sinus infection, *Ann. Otol., Rhin., and Laryng.*, 1934, xliii, 658.
24. SMITH, M. H. D., WILSON, P. E., and HODES, H. L.: The treatment of influenzal meningitis, *Jr. Am. Med. Assoc.*, 1946, cxxx, 331.
25. ALEXANDER, H. E., ELLIS, C., and LEIDY, G.: Treatment of type-specific *Hemophilus influenzae* infections in infancy and childhood, *Jr. Pediat.*, 1942, xx, 673.
26. SAKO, W., STEWART, C. A., and FLEET, J.: Treatment of influenzal meningitis with sulfadiazine; further report, *Jr. Pediat.*, 1944, xxv, 114.
27. TURNER, E. K.: A further report on the treatment at the Children's Hospital, Melbourne, of influenzal meningitis with sulphonamides and type-specific serum, *Med. Jr. Australia*, 1945, i, 219.
28. BECK, K. H., and JANNEY, F. R.: Alexander's rabbit serum in the treatment of influenzal meningitis. An evaluation of its use in conjunction with sulfonamide compounds, *Ann. Jr. Dis. Child.*, 1947, lxxiii, 317.
29. FLEMING, A.: On antibacterial action of cultures of a *Penicillium*, with special reference to their use in isolation of *B. influenzae*, *Brit. Jr. Exper. Path.*, 1929, x, 226.
30. HEWITT, W. L., and PITTMAN, M.: Antibacterial action of penicillin, penicillin X and streptomycin on *Hemophilus influenzae*, *Pub. Health Rep.*, 1946, lxi, 768.
31. GORDON, M., and ZINNEMANN, K.: The in vitro sensitivity of *H. influenzae* to penicillin. With special reference to meningeal strains of Pittman's type b, *Brit. Med. Jr.*, 1945, ii, 795.
32. ZINNEMANN, K.: A survey of the outcome of 20 cases of *H. influenzae* meningitis related to bacterial type, *Brit. Med. Jr.*, 1946, ii, 931.
33. BONABA, J., SURRACO, N. L., PORTILLO, J. M., and SCOLPINI, V.: Meningitis a bacilos de Pfeiffer tratada con penicilina, *Arch. de pediat. d. Uruguay*, 1944, xv, 653.
34. BONABA, J., SURRACO, N. L., CARITAT, J., SOLOVEY, G., and FONSECA, D.: Tres nuevos casos de curacion de meningitis por bacilos de Pfeiffer en lactantes, tratados con la asociacion medicamentosa sulfonamide-penicilina, *Arch. de pediat. d. Uruguay*, 1945, xvi, 137.
35. FORGACS, P., HUTCHINSON, R. I., and REWELL, R. E.: Penicillin sensitivity of *Haemophilus influenzae*; two sensitive pathogenic strains, *Lancet*, 1945, i, 785.
36. MCINTOSH, D. G., and DRYSDALE, C. F.: Meningitis due to a penicillin and sulphonamide sensitive Pittman b strain of *H. influenzae*: Recovery, *Brit. Med. Jr.*, 1945, ii, 796.
37. TURNER, E. K.: Report of a case of resistant *Haemophilus influenzae* meningitis responding to penicillin, *Med. Jr. Australia*, 1947, i, 205.
38. DRYSDALE, C. F., MCINTOSH, D. G., and BRODIE, J.: Meningitis due to a penicillin sensitive, sulphonamide insensitive Pittman b strain of *H. influenzae*: Recovery, *Brit. Med. Jr.*, 1946, ii, 223.
39. ALEXANDER, H. E., and LEIDY, G.: Influence of streptomycin on type b *Haemophilus influenzae*, *Science*, 1946, civ, 101.
40. MURRY, R., PAINE, T. F., and FINLAND, M.: Streptomycin. I. Bacteriologic and pharmacologic aspects, *New England Jr. Med.*, 1947, ccxxxvi, 701.
41. BUTLER, L. J., YOW, M. D., and REINHART, J. B.: Meningitis due to *Hemophilus influenzae*; report of case treated with sulfadiazine, streptomycin and anti-serum, with recovery, *North Carolina Med. Jr.*, 1946, vii, 8.
42. BIRMINGHAM, J. R., KAYE, R., and SMITH, M. H. D.: Streptomycin in the treatment of influenzal meningitis, *Jr. Pediat.*, 1946, xxix, 1.
43. NUSSBAUM, S., GOODMAN, S., ROBINSON, C., and RAY, L.: Influenzal meningitis. Report of three cases treated with streptomycin and sulfadiazine, *Jr. Pediat.*, 1946, xxix, 14.

44. WEINSTEIN, L.: The treatment of meningitis due to *Haemophilus influenzae* with streptomycin. A report of nine cases, New England Jr. Med., 1946, ccxxxv, 101.
45. CAIRNS, M., DUTHIE, E. S., and SMITH, H. V.: Intrathecal streptomycin in meningitis. Clinical trial in tuberculous, coliform and other infections, Lancet, 1946, ii, 153.
46. MORGAN, H. J., and HUNT, J. S.: Streptomycin in clinical practice; a review and case reports, Am. Pract., 1946, i, 73.
47. ZANTINY, W. C., and CARLSON, H. J.: Experiences with streptomycin: Effectiveness in infections of infants and children, Clinics, 1946, v, 635.
48. LOGAN, G. B., and HERRELL, W. E.: Streptomycin in the treatment of influenzal meningitis of children, Proc. Staff Meet. Mayo Clin., 1946, xxi, 393.
49. ALEXANDER, H. E., LEIDY, G., RAKE, G., and DONOVICK, R.: *Hemophilus influenzae* meningitis treated with streptomycin, Jr. Am. Med. Assoc., 1946, cxxxii, 434.
50. HOYNE, A. L., BROWN, R. N., and DRUCKER, A. P.: Influenzal meningitis treated with streptomycin: Report of 3 cases with recoveries, Arch. Pediat., 1946, lxiii, 559.
51. NEVIUS, W. B.: Recovery from influenzal meningitis following treatment with streptomycin, Brooklyn Hosp. Jr., 1947, v, 28.
52. ALEXANDER, H. E., and LEIDY, G.: The present status of treatment for influenzal meningitis, Am. Jr. Med., 1947, ii, 457.
53. Committee on Chemotherapeutics and Other Agents, National Research Council: Streptomycin in the treatment of infections. A report of 1,000 cases, Jr. Am. Med. Assoc., 1946, cxxxii, 4 and 70.
54. ALEXANDER, H. E., and LEIDY, G.: Mode of action of streptomycin on type b *H. influenzae*. I. Origin of resistant organisms, Jr. Exper. Med., 1947, lxxxv, 329.
55. KLEIN, M., and KIMMELMAN, L. J.: The rôle of spontaneous variants in the acquisition of streptomycin resistance by the Shigellae, Jr. Bact., 1946, lii, 471.
56. MILLER, C. P.: Some observations on the development of resistance to streptomycin, Trans. Assoc. Am. Phys., 1947, in press.
57. PAINE, T. F., MURRAY, R., HARRIS, H. W., and FINLAND, M.: Streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system, Am. Jr. Med. Sci., 1947, ccxii, 676.
58. BARRETT, G. S., RAMMELKAMP, C. H., and WORCESTER, J.: Meningitis due to *Escherichia coli*. Report of two cases with recovery following chemotherapy, review of the literature and report of experimental studies, Am. Jr. Dis. Child., 1942, lxiii, 41.
59. BARRON, M.: Meningitis in the newborn and in early infancy, Am. Jr. Med. Sci., 1918, clvi, 358.
60. RAYID, J. M.: Meningococcic and nonmeningococcic meningitis in the newborn and in young infants, Am. Jr. Dis. Child., 1935, xlix, 1282.
61. JAFFE, S. A.: Extrapulmonary *Klebsiella pneumoniae* infections. An analysis of the literature: Report of two unusual cases with recovery, Jr. Am. Med. Assoc., 1943, cxxii, 292.
62. TARTAKOFF, S., GRYNBAUM, B., and Lecompte, P. M.: Friedländer-bacillus meningitis treated with streptomycin, New England Jr. Med., 1946, ccxxxv, 681.
63. STUART, B. M., and PULLEN, R. L.: Tularemic meningitis. Review of the literature and report of a case with postmortem observations, Arch. Int. Med., 1945, lxxvi, 163.
64. McKEE, T. L.: *Bacillus proteus* infections: Review of literature and report of case of septicemia of otitic origin treated with sulfapyridine with recovery, Arch. Otolaryng., 1944, xxxix, 398.
65. DeBAKEY, M. E., and PULASKI, E. J.: An analysis of the experience with streptomycin in United States Army Hospitals. Preliminary report, Surgery, 1946, xx, 749.
66. STANLEY, M. M.: *Bacillus pyocyaneus* infections. A review, report of cases and discussion of newer therapy including streptomycin, Am. Jr. Med., 1947, ii, 253 and 347.
67. NETER, E. R.: *Salmonella cholerae suis* meningitis. Report of a case and review of the literature on *Salmonella* meningitis, Arch. Int. Med., 1944, lxxiii, 425.

68. ARONSON, J. D., and ALDERMAN, I.: The occurrence and bacteriological characteristic of *S. marcescens* from a case of meningitis, Jr. Bact., 1943, xlii, 261.
69. COURVILLE, C. B., and ROSENVOLD, L. K.: Intracranial complications of infections of nasal cavities and accessory sinuses. A survey of lesions observed in a series of 15,000 autopsies, Arch. Otolaryng., 1938, xxvii, 692.
70. BURMAN, H. J., ROSENBLUTH, M., and BURMAN, D.: Otorhinogenic meningitis. A report of 58 cases, Arch. Otolaryng., 1942, xxxv, 687.
71. WOOD, W. H., MAYFIELD, F. H., and FRISCH, A. W.: Meningitis due to *Salmonella panama*, Jr. Am. Med. Assoc., 1945, cxxviii, 868.
72. STRONG, P. S., and EDWARDS, J. E.: *Escherichia coli* meningitis treated with sulfadiazine, Jr. Am. Med. Assoc., 1945, cxxix, 210.
73. HARRIS, R. C., BUXBAUM, L., and APPELBAUM, E.: Secondary *Bacillus pyocyaneus* infection in meningitis following intrathecal penicillin therapy, Jr. Lab. and Clin. Med., 1946, xxxi, 1113.
74. EDWARDS, M. W., and KIRK, G. D.: Development of resistance to streptomycin by *Aerobacter cloacae*, Am. Jr. Clin. Path., 1946, xvi, 527.
75. ALEXANDER, A. J.: Meningitis due to *Escherichia coli* treated with streptomycin, Jr. Am. Med. Assoc., 1946, cxxxi, 663.
76. SHIELDS, W. P.: Meningitis due to *Escherichia coli*. Streptomycin therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 514.
77. BARNES, M.: *Salmonella* meningitis. Report of a case treated with streptomycin, Bull. Charlotte Memorial Hosp., 1946, ii, 44.
78. MASSENGALE, L. R.: Paratyphoid B meningitis in an infant; report of a case, Jr. Med. Assoc. Georgia, 1946, xxxv, 345.
79. SCHATZ, A., and WAKSMAN, S. A.: Effect of streptomycin and other antibiotic substances upon *Mycobacterium tuberculosis* and related organisms, Proc. Soc. Exper. Biol. and Med., 1944, lvii, 244.
80. FELDMAN, W. H., and HINSHAW, H. C.: Effects of streptomycin on experimental tuberculosis in guinea pigs. A preliminary report, Proc. Staff Meet. Mayo Clin., 1944, xix, 593.
81. YOUMANS, G. P.: The effect of streptomycin in vitro on *M. tuberculosis var. hominis*, Quart. Bull. Northwestern Univ. Med. School, 1945, xix, 207.
82. YOUMANS, G. P., and FELDMAN, W. H.: The sensitivity of tubercle bacilli in vitro to streptomycin, Jr. Bact., 1946, li, 608.
83. MIDDLEBROOK, G., and YEGIAN, D.: Certain effects of streptomycin on mycobacteria in vitro, Am. Rev. Tuberc., 1946, liv, 553.
84. ANDERSON, D. G., and JEWELL, M.: The absorption, excretion and toxicity of streptomycin in man, New England Jr. Med., 1945, cxxxiii, 485.
85. REIMANN, H. A., PRICE, A. H., and ELIAS, W. F.: Streptomycin for certain systemic infections and its effect on the urinary and fecal flora, Arch. Int. Med., 1945, lxxvi, 269.
86. COOKE, R. E., DUNPHY, D. L., and BLAKE, F. G.: Streptomycin in tuberculous meningitis; a report of its use in a one-year-old infant, Yale Jr. Biol. and Med., 1946, xviii, 221.
87. THOMPSON, J. L., and WAGENHEIM, H. H.: The use of streptomycin in acute military tuberculosis. Report of a case, Med. Ann. District of Columbia, 1946, xv, 265.
88. BORNSTEIN, P. K.: Streptomycin in military tuberculosis with tuberculous meningitis. Case report with autopsy findings, Quart. Bull. Sea View Hosp., 1946, viii, 219.
89. KRAFCHIK, L. L.: Tuberculous meningitis treated with streptomycin, Jr. Am. Med. Assoc., 1946, cxxxii, 375.
90. HINSHAW, H. C., FELDMAN, W. H., and PFUETZE, K. H.: Treatment of tuberculosis with streptomycin. A summary of observations on one hundred cases, Jr. Am. Med. Assoc., 1946, cxxxii, 778.

91. DAVENPORT, L. F.: Streptomycin in pulmonary tuberculosis, Bull. New England Med. Center, 1947, ix, 83.
92. BAGGENSTOSS, A. H., FELDMAN, W. H., and HINSHAW, H. C.: Streptomycin in miliary tuberculosis: its effect on pathological lesions of generalized miliary tuberculosis in human beings, Am. Rev. Tuberc., 1947, lx, 54.
93. YOUMANS, G. P., WILLISTON, E. H., FELDMAN, W. H., and HINSHAW, H. W.: Increase in resistance of tubercle bacilli to streptomycin: A preliminary report, Proc. Staff Meet. Mayo Clin., 1946, xxi, 126.
94. KARLSON, A. G., FELDMAN, W. H., and HINSHAW, H. C.: Persistence of resistance of tubercle bacilli to streptomycin during passage through guinea pigs, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 6.
95. CALLOMON, F. T., KOLMER, J. A., RULE, A. M., and PAUL, A. J.: Streptomycin and diasone in the treatment of experimental tuberculosis of guinea pigs, Proc. Soc. Exper. Biol. and Med., 1946, lxiii, 237.
96. SMITH, M. I., McCLOSKEY, W. T., JACKSON, E. L., and BAUER, H.: Chemotherapeutic action of streptomycin and of streptomycin with a sulfone or sulfadiazine on tuberculosis, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 261.
97. KLEIN, M., and KIMMELMAN, L. J.: Synergism and inhibition of drug resistance, (Abstract), Proc. Am. Soc. Bact., 1947, p. 8 (May).
98. JOHNSON, H. C., WALKER, A. E., CASE, T. J., and KOLLROSS, J.: Effects of antibiotic substances on the central nervous system, Arch. Neurol. and Psychiat., 1946, lvi, 184.
99. FISHBURN, G. W., FISHER, M. W., and WALLACE, J. B.: Some observations in the use of streptomycin in the treatment of tuberculosis of various types, to be published.
100. ERICKSON, T. C., MASTEN, M. G., and SUCKLE, H. M.: Complications of intrathecal use of penicillin, Jr. Am. Med. Assoc., 1946, cxxxii, 561.
101. NEILL, C. L., and BLECHMAN, H. E.: *Aerobacter aerogenes* meningitis, Bull. U. S. Army Med. Dept., 1947, vii, 722.
102. HOUGH, P. T., and ADELSON, L.: Meningitis caused by Friedlander's bacillus of *Aerobacter aerogenes*. Report of two cases with autopsies, Am. Jr. Clin. Path., 1947, xvii, 534.
103. MERWARTH, H. R., ROSENBERG, M., and PULITO, F.: Pyocyanus meningitis followed by unusual complications attributed to treatment with streptomycin, Brooklyn Hosp. Jr., 1947, v, 93.
104. PULASKI, E. J., and MATTHEWS, C. S.: Streptomycin in surgical infections. III. Otitis externa, otitis media, mastoiditis, brain abscess and meningitis, Arch. Otolaryng., 1947, xlv, 503.

# PLEUROPULMONARY TULAREMIA \*

By HUGH J. MORGAN, M.D., F.A.C.P., *Nashville, Tennessee*

IN a previous communication to the ANNALS OF INTERNAL MEDICINE from the Vanderbilt University Hospital, Hunt reported observations on 12 cases of pleuropulmonary tularemia treated with streptomycin during a nine months period in 1946.<sup>1</sup> Unfortunately, the clinical charts prepared for this publication were lost by the printer and did not appear in Hunt's article.

In the present communication selected cases from the Vanderbilt University Hospital material and 15 additional cases of pleuropulmonary tularemia treated with streptomycin in Veterans Administration Hospitals are presented in summary form and discussed briefly. For a more detailed discussion of pleuropulmonary tularemia the reader is referred to the excellent article and bibliography by Hunt.

## UNCOMPLICATED ULCEROGLANDULAR TULAREMIA

This common form of tularemic infection constitutes no diagnostic problem. The occurrence of ulcer or localized inflammatory process at the site of inoculation (finger, hand, eye) with satellite bubo, a sharp febrile reaction often accompanied by chill and the history of contact exposure (most commonly by having dressed a wild rabbit during the preceding week or 10 days) leave little doubt as to the nature of the infection. The response to streptomycin therapy is prompt.

*Case 1 (Figure 1) D. B. Ulceroglandular tularemia.* A 17 year old colored male dressed a wild rabbit seven days before the development of an ulcer on the dorsum of the right hand, chill, fever, severe headache and prostration. A week later he was admitted to the Nashville General Hospital acutely ill. The ulcer was indurated. The right epitrochlear and axillary lymph nodes were large and tender. Fever was present. The leukocyte count was normal. The serum agglutination titer against *P. tularensis* was 1:40 and subsequently rose to 1:5120. *P. tularensis* was recovered from an epitrochlear node by mouse inoculation. The administration of streptomycin (1 gm. daily, in divided doses, for four days) was followed by prompt relief of symptoms and gradual disappearance of fever. Five days after termination of streptomycin treatment material aspirated from the epitrochlear lymph node failed to yield *P. tularensis* on mouse inoculation. The ulcer healed slowly and there was slow regression in the size of the lymph nodes. Recovery was complete.

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I am indebted to Drs. Aubrey B. Harwell and Robert C. Berson of the Thayer Veterans Hospital, Nashville, Tennessee, and the Veterans Administration, Washington, D. C., for the data on patients in Veterans Administration hospitals.

ULCEROGLANDULAR TULAREMIA WITH COMPLICATIONS

When in the course of ulceroglandular tularemia manifestations of infection develop elsewhere, as in the pleura, lungs, pericardium and central nervous system, there is reason for little doubt regarding the etiology of the complications. The recognition of the tularemic etiology of the ulceroglandular lesions clarifies the problem of the complications. The incidence of pleuropulmonary complications in patients with ulceroglandular tularemia who were admitted to Veterans Administration Hospitals during a nine

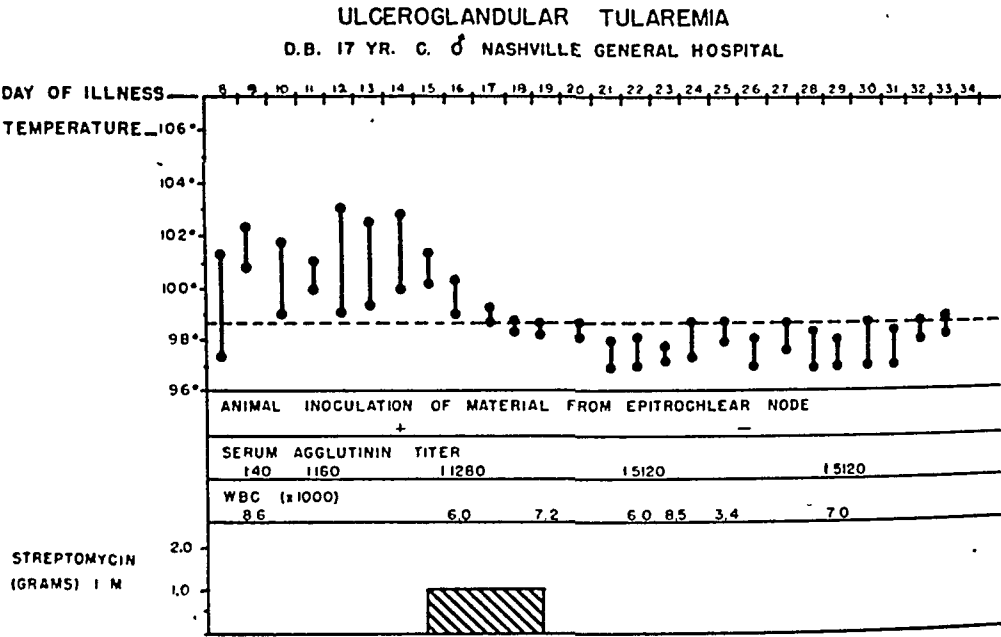


FIGURE 1.

months period in 1946 is indicated in table 1. They were present in more than 25 per cent of the patients. The extraordinary effectiveness of streptomycin in the presence of such complications is apparent in Cases 2 and 3. In both instances the patients were desperately ill.

TABLE I  
Incidence of Pleuropulmonary Involvement in Tularemia  
(Veterans' Administration Hospitals, 9 mo., 1946)

Pleuropulmonary Involvement	Number	Per Cent
Absent	41	73
Present	15	27
Total	56	100

Case 2. (Figure 2) L. V. Ulceroglandular tularemia with pneumonia, pleural effusion and pericarditis. A 28 year old white farmer cut his hand while dressing a wild rabbit 14 days before admission to hospital. Four days later multiple ulcers on the hand, fever and prostration developed. On the fourth day of fever, cough pro-

ductive of yellow sputum was noted and he appeared to be losing ground. On the eleventh day of illness he was admitted to the Vanderbilt University Hospital in a semi-comatose state. There was moderate dyspnea. A loud pericardial friction rub was heard and fluid was present in the left pleural cavity. There were three small, shallow, indurated ulcers on the left hand and the left epitrochlear lymph node was large and tender, as were the left posterior cervical lymph nodes. Purulent conjunctivitis was present. The spleen was palpable. The leukocyte count was 4600.

Sputum obtained on admission, before the administration of streptomycin, was injected into mice. *P. tularensis* was subsequently recovered. The patient's blood serum contained no agglutinins against *P. tularensis*.

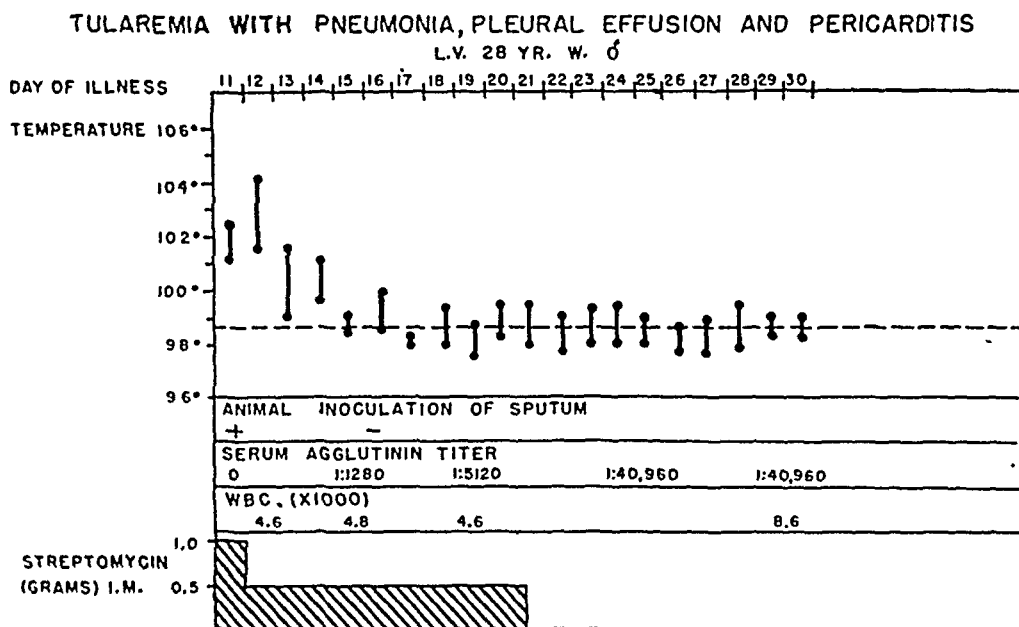


FIGURE 2.

During the first 24 hours in hospital the patient received 1 gm. streptomycin in divided doses. Within 12 hours he became mentally alert and appeared greatly improved. Streptomycin was continued in daily doses of 0.5 gm. After 48 hours the temperature declined moderately, there was striking improvement in the conjunctivitis and the lymph nodes were less tender. He coughed less and the sputum became mucoid. The pericardial friction rub disappeared. On the fourth hospital day 1250 c.c. of serosanguinous fluid were removed from the left pleural cavity. Specimens of this fluid and of sputum were injected into mice, all of which survived. Following the thoracentesis the physical signs indicated the presence of consolidation of the lower lobe of the left lung. Streptomycin 0.5 gm. daily in divided doses was continued for a total of 11 days because of the persistence of slight fever. At the time of discharge from the hospital there was still a moderate amount of fluid in the left pleural cavity. The spleen was no longer palpable. The serum agglutination titer had risen to 1:40,960. Two months later he was well and at work. A roentgenographic examination of the chest revealed only residual pleural thickening.

Case 3. (Figure 3) J. E. Ulceroglandular tularemia; bronchopneumonia; encephalitis. This 67 year old white farmer dressed a wild rabbit nine days before the appearance of an ulcer on the right thumb and the development of chill, high fever and severe headache. Within 24 hours he had pleural pain and a nonproductive



cough. He was admitted to the St. Thomas Hospital on the service of Dr. B. H. Webster on the sixth day of illness in a semistuporous state.

When aroused he complained bitterly of headache. An indurated ulcer was present on the left thumb and the left epitrochlear and axillary lymph nodes were large and tender. Many fine moist râles were heard over both lung fields and a roentgenogram revealed diffuse bilateral bronchopneumonia. The leukocyte count was 10,600.

### TULAREMIC PNEUMONIA. TULAREMIC ENCEPHALITIS (?)

J. E. 67 YR. W. ♂ ST. THOMAS HOSPITAL

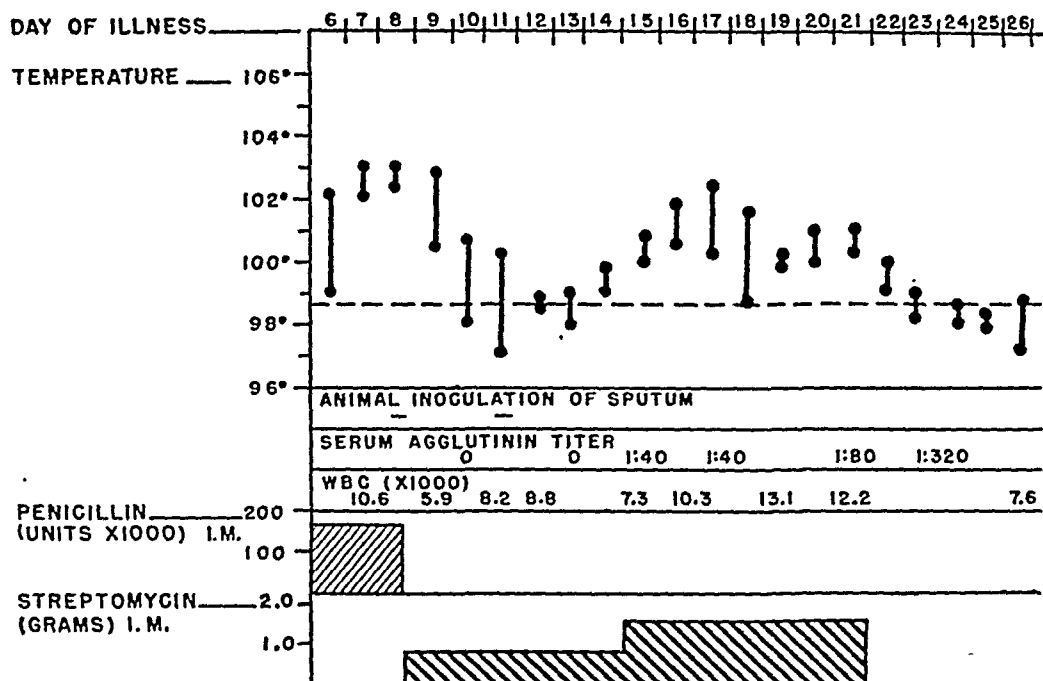


FIGURE 3.

A clinical diagnosis of tularemic infection was made. Streptomycin was not immediately available. Treatment with penicillin was not effective. Stupor deepened and he became incontinent of urine and feces. Bilateral Babinski signs appeared. No agglutinins against *P. tularensis* were present in the serum, and sputum which was injected into mice failed to produce tularemic infection. Streptomycin treatment was begun on the third hospital day in doses of 0.8 gm. daily, intramuscularly in divided doses at four-hour intervals. The temperature gradually fell to normal in a period of five days, clearing of the pneumonia was demonstrated by roentgen-ray examination and the ulcer and lymphadenopathy exhibited improvement. However, stupor continued and the temperature again rose. On the fourteenth day of illness (ninth hospital day) the cerebrospinal fluid was found to be under normal pressure and contained 20 mg. of protein. The cell count was 29 per cu. mm. and the majority of cells were granulocytes. The dose of streptomycin was increased to 1.6 gm. per day. Within 48 hours the patient exhibited marked improvement. He became mentally alert and was free of headache. Serum agglutinins against *P. tularensis* were demonstrated for the first time on the fifteenth day of illness. Streptomycin was continued for a total of two weeks' treatment. The temperature gradually fell to normal values. The Babinski signs disappeared. The serum agglutinin titer rose

to 1:320. On the twenty-third day of illness a second cerebrospinal fluid examination revealed 2 leukocytes per cu. mm. The protein content was 60 mg. per 100 c.c. The patient was seen six weeks following his discharge from the hospital. He was in good health. The serum agglutinin titer was 1:320.

*Comment:* The failure to recover *P. tularensis* from the sputum by mouse inoculation is attributed to faulty technic in the collection of the specimen. The appearance of agglutinins in the serum and the response of the ulceroglandular and pulmonary lesions to streptomycin confirmed the clinical diagnosis of tularemic infection. The nature of the cerebral complication was not clear. The clinical picture and the improvement following larger doses of streptomycin suggest that tularemic lesions were present in the brain.

### TULAREMIC INFECTION IN THE ABSENCE OF ULCEROGLANDULAR LESIONS (Cryptogenic infection)

As indicated above the recognition of tularemic infection, with or without pulmonary involvement, poses no problem when the typical primary ulcer and regional buboes are present. In the absence of these tell-tale lesions the clinical picture is obscure and etiologic diagnosis must attend upon either the demonstration of the organism by culture or animal inoculations, or the development of specific agglutinins in the blood serum. The former diagnostic procedure is dangerous and time-consuming. Specific agglutinins do not appear until the end of the second or during the third week of tularemic infection. Thus, patients with severe tularemic infections may die before an accurate etiologic diagnosis can be established by these laboratory methods.

The incidence of pleuropulmonary tularemia in the absence of ulceroglandular lesions is indicated by table 2. Over half of the Vanderbilt and

TABLE II  
Incidence of Ulceroglandular Lesions in Pleuropulmonary Tularemia  
(V.U. Hospital and Vet. Ad. Hospitals)

Ulceroglandular Lesions	Number	Per Cent
Absent	16	59
Present	11	41
Total	27	100

Veterans Administration patients had no ulceroglandular lesions and presented themselves with pleuropulmonary infections of unknown etiology. Thus, primary atypical pneumonia of unknown etiology, viral pneumonia of known etiology (influenza, psittacosis, lymphogranuloma venereum, lymphocytic choreomeningitis) and tuberculous infection were considered originally as diagnostic possibilities.

Cases 4, 5, and 6 are examples of pleuropulmonary infection due to *P. tularensis* which, since they occurred in the absence of the classical ulceroglandular lesions, constituted difficult diagnostic problems.

Case 4. (Figure 4) *H. H. Tularemic pneumonia; pleural effusion.* This 37 year old business man developed high fever, pleural pain and prostration 10 days before admission to the Vanderbilt University Hospital. Sulfathiazole treatment for pneumonia was administered without benefit for six days. Then sulfathiazole was replaced by sulfadiazine and penicillin was begun. Four days before admission to the hospital a pleural friction rub and fine moist râles were heard over the right lung and he seemed much worse.

### TULAREMIC PNEUMONIA WITH PLEURAL EFFUSION

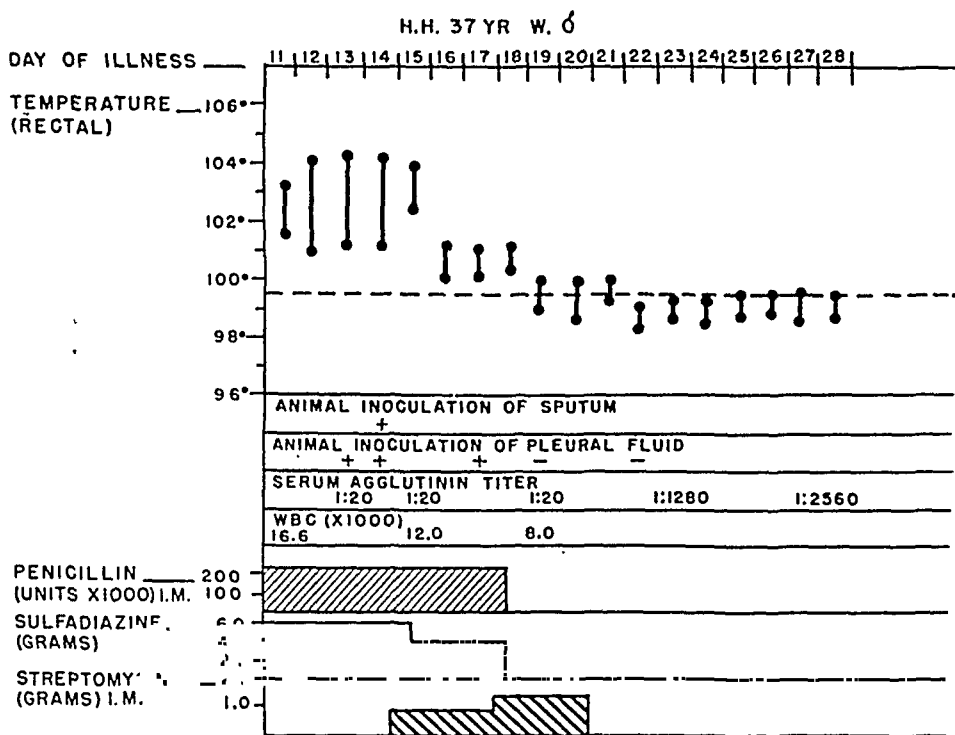


FIGURE 4.

On admission to the hospital he appeared desperately ill. High fever was present and he was dyspneic and cyanotic. The skin and superficial lymph nodes were normal. The physical signs of pneumonia and left pleural effusion were confirmed by roentgen-ray examination. The area of consolidation was in the hilar region. The leukocyte count was 16,600. Microscopic examinations of the sputum revealed few organisms of any kind. A tentative diagnosis of severe primary atypical pneumonia was made and treatment with penicillin and sulfadiazine was continued. Thoracentesis yielded 60 c.c. of sanguinous fluid containing 12,000 leukocytes per cu. mm. Cultures of this fluid by routine methods produced no growth. On the fourteenth day of illness he became stuporous. A second thoracentesis yielded 450 c.c. of dark bloody fluid. The possibility of cryptogenic tularemic infection was considered. Members of the family stated that there had been no exposure to wild rodents. It was recalled that he had removed ticks from his dog on several occasions prior to the development of the present illness. A therapeutic trial with streptomycin was decided upon. Before the administration of streptomycin specimens of sputum and pleural fluid were injected into mice. All of the mice died and *P. tularensis* was cultured from their spleens. An agglutination titer of the patient's serum against *P. tularensis* of 1:20 was reported.

On the fourteenth day of illness streptomycin treatment was begun, 0.8 gm. daily, intramuscularly in divided doses at four hour intervals. The following day the temperature was somewhat lower and the patient's mental state was clearer. Forty-eight hours later marked improvement was noted. There was much less dyspnea and cyanosis. On the third day of streptomycin treatment the dose was increased to 1.6 gm. Four hundred and fifty c.c. of pleural fluid were aspirated. Specimens were injected into mice which again yielded *P. tularensis*. Nevertheless, the patient improved steadily and streptomycin treatment was terminated after seven days. Specimens of pleural fluid obtained after the fifth day of streptomycin treatment failed to infect mice. The serum agglutinin titer rose from 1:20 to 1:2560. When seen one month after his discharge from the hospital the patient felt well. Fluoroscopic examination of the chest showed residual pleural thickening.

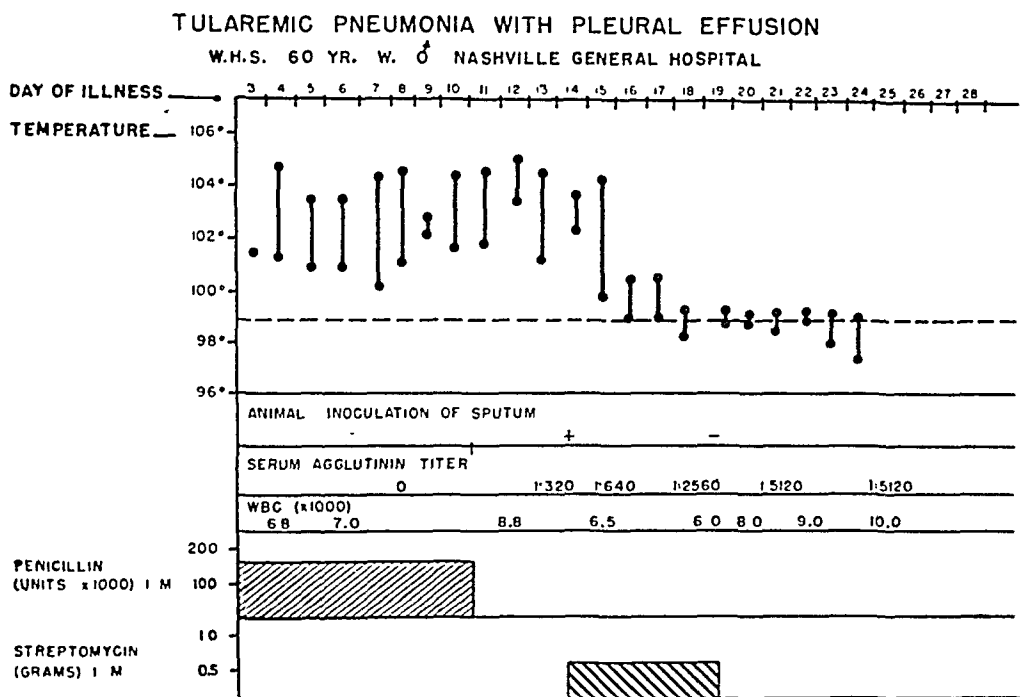


FIGURE 5.

*Case 5. (Figure 5) W. H. S. Tularemic pneumonia with pleural effusion.* Two days before admission to the Nashville General Hospital this 60 year old farmer experienced a shaking chill associated with fever and prostration. He soon became delirious. On admission to the hospital he was semi-stuporous. The skin was normal and there was no enlargement of the superficial lymph nodes. Two small shallow dirty ulcers were present on the pharyngeal pillars. Physical signs over the lower lobe of the right lung indicated an area of consolidation and roentgen-ray examination confirmed the presence of bronchopneumonia. The spleen was not palpable. The leukocyte count was 6800. Penicillin treatment was instituted without effect upon the illness. He continued to have high fever and stupor deepened. On the seventh day of the illness diarrhea developed and persisted during the following week. The presence of a small pleural effusion was noted. Serum agglutinins against *P. tularensis* were absent on the eighth day of the illness but were present on the fourteenth day 1:320. Sputum obtained at this time yielded *P. tularensis* on mouse inoculation. Streptomycin 0.6 gm. daily in divided doses intramuscularly at four hour intervals

was begun. Within 24 hours he became rational and alert. The diarrhea ceased. The temperature fell abruptly to lower values and within four days became normal. The pharyngeal ulcers healed. Prior to and during the period of streptomycin therapy the amount of fluid in the right pleural cavity slowly increased and on the day the antibiotic was discontinued 1000 c.c. of serosanguinous fluid were removed. Specimens of this fluid failed to produce infection when injected into mice. The fluid did not reaccumulate and the patient was discharged from the hospital, apparently well.

### TULAREMIC PLEURISY

H.G. 36 YR. W. ♂

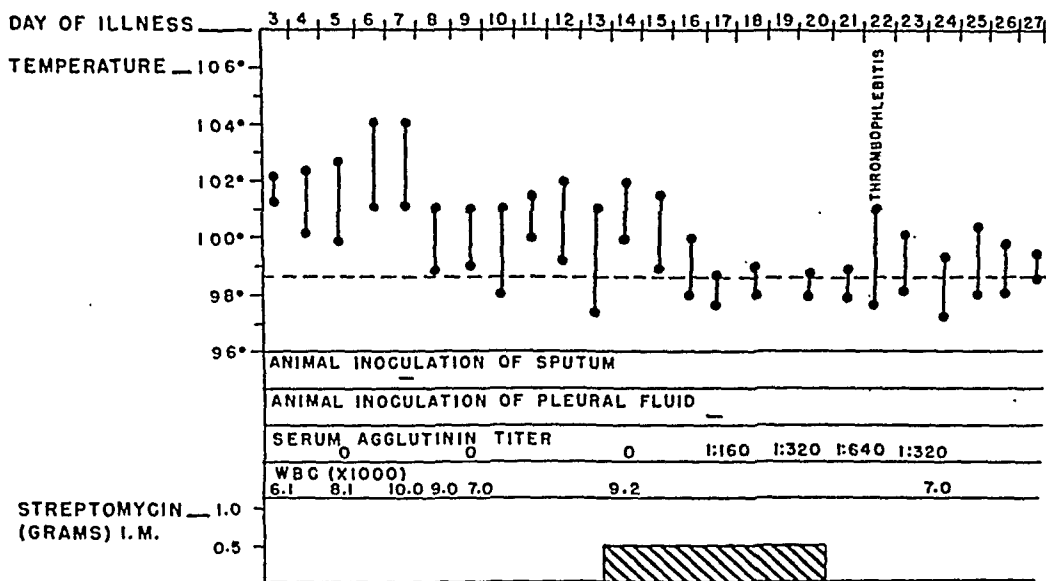


FIGURE 6.

*Case 6 (Figure 6) H. G. Acute tularemic pleurisy.* A 36 year old farmer was admitted to the Vanderbilt Hospital on the third day of an acute illness initiated by chill, fever, and epigastric pain. The latter was aggravated by coughing.

He appeared acutely ill. The skin and superficial lymph nodes were normal. The lungs were clear. There was marked epigastric tenderness and voluntary muscle spasm. The spleen was felt one finger's breadth below the costal margin. The leukocyte count was 6100. A roentgen-ray examination of the chest revealed no abnormalities.

During the first week of hospitalization the patient had high remittent fever. A pleural friction rub developed over the left chest and on the seventh day of illness there were signs suggestive of a left pleural effusion. A thoracentesis yielded no fluid. A pneumothorax, induced at the time of the thoracentesis, relieved the pleuritic pain. The possibility of tularemic infection was considered. The patient denied contact with wild rodents but during his work as a woodcutter he had repeatedly removed ticks from his skin. No serum agglutinins against *P. tularensis* were present on the fifth, ninth and fourteenth days of illness. Nevertheless, on the fourteenth day, streptomycin treatment was begun as a therapeutic trial. One-half gm. daily was administered in divided doses at four hour intervals. In 24 hours malaise had disappeared and he said that he felt perfectly well. Within four days the temperature became normal. On the third day of streptomycin therapy (sixteenth day of illness) 8 c.c. of straw-colored fluid were aspirated from the left pleural cavity and injected into

mice. All survived. The following day agglutinins against *P. tularensis* were demonstrated in the serum for the first time, in a dilution of 1:160. During the next week there was a progressive rise in the titer to 1:640. The pleural effusion gradually disappeared. Convalescence was complicated by the development of left femoral thrombophlebitis. Recovery was complete.

*Comment:* It seems highly probable that patients H. H. and H. G. (Cases 4 and 6) were infected with *P. tularensis* as a result of contacts with ticks. Patient W. H. S. (Case 5) may represent infection by the oral route, the ulcers of the pharyngeal mucous membrane constituting the primary lesions. However this may be, the nature of the infection was obscure in each instance and as a result specific, curative treatment was delayed. Patients H. H. and H. G. were desperately ill. It is entirely possible that further delay in the administration of specific therapy would have proved fatal.

The extraordinary effectiveness of streptomycin in the treatment of tularemic infections is indicated in the combined experience of the Vanderbilt Hospital and the Veterans Administration Hospitals. Twenty-seven patients with tularemic pleuropulmonary infection were treated. Only one death occurred and this is believed to have resulted from pulmonary artery embolism during convalescence from the pulmonary infection.

TABLE III  
Pleuropulmonary Tularemia Treated with Streptomycin

	Number	Recovery	Death
Vanderbilt University Hospital	12	11	1
Veterans' Administration Hospitals	15	15	0
Total	27	26	1

### SUMMARY

More than one-fourth of the tularemic infections observed in Veterans Administration Hospitals during a nine month period in 1946 had pleuropulmonary involvement.

Only 40 per cent of patients in the Vanderbilt and Veterans hospitals group with pleuropulmonary tularemic infection had tell-tale ulceroglandular lesions. Thus, more than half presented themselves as obscure pulmonary infections or masqueraded as primary atypical pneumonia of unknown etiology. Under such circumstances, even when the possibility of tularemic infection is considered and diagnostic tests for its presence are employed, the clinician is seriously handicapped, for the demonstration of *P. tularensis* in culture or by mouse inoculation is time consuming and dangerous, and diagnostic agglutinins do not appear in the patient's blood until the end of the second or during the third week of infection.

Streptomycin is curative in pleuropulmonary tularemia, the pre-streptomycin mortality of which was from 20 to 40 per cent. In suspect cases

a therapeutic trial with streptomycin, as recommended by Hunt, may save life in an infection which sometimes kills before the appearance of serum agglutinins and before culture or mouse inoculation yields the causative organism. Administration of streptomycin does not inhibit the subsequent appearance of diagnostic agglutinins. Therefore, a therapeutic trial with streptomycin is indicated in critically ill individuals suspected of having severe primary atypical pneumonia or other forms of viral pneumonia, when the illness is of less than two weeks' duration and when it occurs in a region where tularemia is endemic.

#### BIBLIOGRAPHY

1. HUNT, J. S.: Pleuropulmonary tularemia: Observations on 12 cases treated with streptomycin, *Ann. Int. Med.*, 1947, xxvi, 263.

# NITROGEN MUSTARD AS A THERAPEUTIC AGENT FOR HODGKIN'S DISEASE, LYMPHOSARCOMA AND LEUKEMIA \*

By MAXWELL M. WINTROBE, F.A.C.P., CHARLES M. HUGULEY, JR.,†  
MARGARET T. McLENNAN and LUCIO PENNA DE CARVALHO  
LIMA,‡ *Salt Lake City, Utah*

THE nitrogen mustards differ from the mustard war gas only in that nitrogen replaces sulfur. Study of the biological effects of the nitrogen mustards has revealed that they parallel and are almost identical with the biological effects of radiant energy.

The most important properties of the beta chloroethyl amines (nitrogen mustards) are outlined in table 1. While these substances are stable and

TABLE I

## Properties of $\beta$ -Chloroethyl Amines (Nitrogen Mustards)

Contact vesicants. *Also* cytotoxic following absorption.

Physiological activity due to the intramolecular cyclization of the compound in a polar solvent to form a cyclic onium cation.

Pronounced nucleotoxic action. Inhibits mitosis. Induces chromosomal abnormalities.

Severity of response directly related to dose used.

Susceptibility of cells related to degree of proliferative activity.

Lymphatic tissue, bone marrow and mucosa of gastrointestinal tract especially susceptible. In large enough doses all cells are affected.

So reactive that effects are over in less than five minutes.

Manner of action possibly related to action on an enzyme system.

unreactive in dry form, in aqueous solution a rapid change takes place. The beta carbon forms a ring with the nitrogen to make a quaternary ammonium base, with the release of chloride ion. The quaternary ammonium ion is highly active and reacts with a variety of biologically important chemical groupings such as amino, carboxyl, sulfhydryl, etc. The intravenous administration of these compounds was found, as the result of investigation carried out during the second world war, to produce almost complete dissolution of lymphoid tissue in 24 hours.<sup>1</sup> The bone marrow is also affected, particularly the granulocytes. With sufficient dosage complete aplasia can be produced. In addition, degenerative changes in the epithelial tissue of the gastrointestinal tract can be produced if very large doses are given, and

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‡ On leave from the University of Sao Paulo, Sao Paulo, Brazil.



even a hemorrhagic enteritis can ensue. If the amount given is great enough, every cell in the body can be affected. These compounds are so reactive that their effects are over within a few minutes. It was observed, for example, that occlusion of circulation to a given area for five minutes afforded complete protection of that area.

The susceptibility of cells to the action of these compounds is related to the proliferative activity of the cells. The effects are similar to those of radiant energy. Mitotic activity is inhibited and chromosomal abnormalities can be induced. The first trial of the nitrogen mustards for the treatment of neoplasms involving the lymphoid and hemopoietic tissues was reported by Gilman, Goodman, Lindskog and Dougherty.<sup>2</sup> Preliminary reports of investigations at the University of Chicago,<sup>3</sup> the University of Utah<sup>4</sup> and elsewhere<sup>5</sup> have now appeared.

### MATERIAL AND METHODS

To date we have used nitrogen mustard in the treatment of 77 cases of Hodgkin's disease, lymphosarcoma, leukemia and certain miscellaneous disorders. In all of these cases the hydrochloride salt of di( $\beta$ -chloroethyl) methyl amine ( $\text{CH}_3\text{N}(\text{C}_2\text{H}_4\text{Cl})_2$ ) was used. The following method of administration has been found to be the most satisfactory. A saline infusion is started and its smooth running into the vein assured. Then to 10 milligrams of the dry white crystalline hydrochloride salt of the mustard, obtainable in small sterile bottles, 10 c.c. of sterile physiologic saline are added. The salt dissolves promptly and the calculated dose of solution is withdrawn into a sterile syringe. This is immediately administered to the patient by injecting it through the rubber tubing of the saline infusion. Care is taken to avoid touching the skin or mucous membranes of the patient or physician with any of the solution although no harm has resulted from accidental spilling when the skin has been washed immediately. It is important that the nitrogen mustard be injected promptly after it has been dissolved as its activity is quickly dissipated. The injection of the concentrated salt through the tubing of the saline infusion allows it to be washed into the veins quickly. The concentrated solution injected into a vein may produce phlebothrombosis, and extravasation into the surrounding tissue can produce necrosis and sloughing.

The dosage used has usually been 0.1 milligram per kilogram body weight. As a rule four to six infusions have been given at intervals of one or two days depending on the presence or absence of severe toxic symptoms. In several cases as many as eight daily infusions have been given and in one patient as much as 0.25 milligram has been given per kilogram body weight per dose. In a few cases, smaller doses have been used. In patients with chronic leukemia or Hodgkin's disease who had already responded to nitrogen mustard therapy, maintenance therapy has been carried

out by giving two or three infusions on successive days at two to four week intervals. This has been done without hospitalizing the patients.

### CLINICAL RESULTS

In table 2 statistical data concerning the cases treated are presented and in table 3 the results of treatment are summarized. The designation, "good" response, has been used if a patient was able to return to his usual occupation for several months or more and was free of troublesome symptoms.

TABLE II  
Statistical Data Concerning Patients Treated with Nitrogen Mustard

Diagnosis	Total No. of Cases	Sex		Age		Duration of Symptoms before Admission		Number Previously Treated with X-ray
		M	F	Range Yrs.	Av. Yrs.	Range Mos.	Av. Mos.	
Hodgkin's disease	28	16	11	14-67	36.3	3-60	23.8	22
Lymphosarcoma	11	6	5	11-82	49.5	1-60	16.4	5
Leukemia ch. myel.	8	4	4	28-58	43	3-48	29.0	5
Leukemia ch. lymph.	10	8	2	45-87	59	1-132	37.0	4
Leukemia acute	8	4	4	2-65	21	6-120 days	52 days	0
Misc.*	12	9	4	22-75	46	1-84	22.6	5

\* Presumptive but unproved Hodgkin's disease 2, metastatic carcinoma 4, multiple myeloma 2, malignant melanoma 1, carcinoma bronchus 1, Kaposi's sarcoma 1, fibrosarcoma (metastatic) 1.

TABLE III  
Results of Treatment with Nitrogen Mustard, 65 Cases

Diagnosis	Total No. of Cases	Nitrogen Mustard		Results			Patients Living		Patients Dead	
		No. of Doses	Total Dosage Mg.	Good	Fair	Poor	No.	Time since 1st Treat. Mos.	No.	Time from Rx to Death Mos.
				Per Cent						
Hodgkin's disease	28	4-40	24-193	61	18	21	15	1-26	12	1-16
Lymphosarcoma	11	1-20	4-120	36	—	64	2	2-5	9	1.5-12
Leukemia, ch. myel.	8*	2-41	12-294	43	14	43	6	1-22	2	1-3
ch. lymph.	10	1-10	7-87	30	10	60	6	1-24	3	3-30 d.
acute	8	3-22	4-64	—	38	62	0		8	0.5-3.5

\* Includes one case with inadequate follow-up.

If there was definite improvement but of a less striking or more short-lived nature the response is termed "fair." In this category have also been placed cases in which striking relief of some particularly distressing symptom such as intractable pain occurred even though the course of the illness was not significantly altered otherwise. Those cases which have shown little if any improvement or in which the improvement lasted for only a few weeks are classified as "poor" responses.

In the cases which have been studied almost all stages and manifestations of the diseases under consideration have been represented. Consequently, it is difficult to offer a final evaluation of results. The comments which will be made must be understood to be of a preliminary character and as offering simply a running account of experience to date.

*Hodgkin's Disease.* In this series of 28 patients, one of the most constant and striking effects of nitrogen mustard was upon fever in those patients who manifested this sign of the disease. With the exception of one case of Hodgkin's sarcoma and one terminal case with secondary infection, the first course of nitrogen mustard caused the temperature to return to normal, and in many patients this effect was repeated many times in subsequent courses. In most cases, along with the beneficial effects upon the fever, there was an increased feeling of well being, improvement in appetite, gain in weight and general clinical improvement. In some patients, the upsurge in appetite following therapy was one of the most striking effects noted. The duration of remissions varied from a few days to several months.

In general, large lymph nodes decreased moderately in size following treatment with nitrogen mustard. In those patients who had enlargement of the spleen, a reduction in the size of this organ usually followed nitrogen mustard therapy. In 19 of our patients with Hodgkin's disease, there was evidence of mediastinal lymph node enlargement or lung parenchyma involvement. In a number of these patients a clear-cut effect on mediastinal widening, extent of parenchymal change, dyspnea and, particularly, on the associated hacking cough was noted. Even dysphagia associated with the presence of a mediastinal mass has been relieved.

The influence of nitrogen mustard on pruritus has varied depending, it seems, on whether or not nitrogen mustard proved effective in the treatment of the disease as a whole. In three patients, back pain constituted one of the most distressing symptoms of the disease. In two of these roentgenographic evidence of bone involvement was present. All three patients obtained dramatic relief following nitrogen mustard therapy. In two patients abdominal pain was relieved following nitrogen mustard therapy.

Nine patients in this series were extremely ill and were responding no longer to roentgen-ray therapy. One of the most striking beneficial effects of nitrogen mustard therapy which we have observed to date has been the remarkable improvement which has occurred in five of these "roentgen-ray resistant" patients (figure 1).

Of the 28 patients with Hodgkin's disease, 15 are living at the present time and 13 are dead. In six patients (21 per cent) the results were definitely poor. In 17 (61 per cent) they may be classified as good, while in 5 (18 per cent) the response could be characterized as only fair. The responses thus have varied greatly and a noteworthy feature is the fact that it seems to be difficult to estimate in advance whether a response will be good

or poor. As already mentioned, several patients who seemed nearly terminal responded surprisingly well. Others, however, even early in the disease showed only a brief response to nitrogen mustard therapy. The remissions in our cases have varied greatly in duration. The longest has been 27 months and the shortest was three weeks.

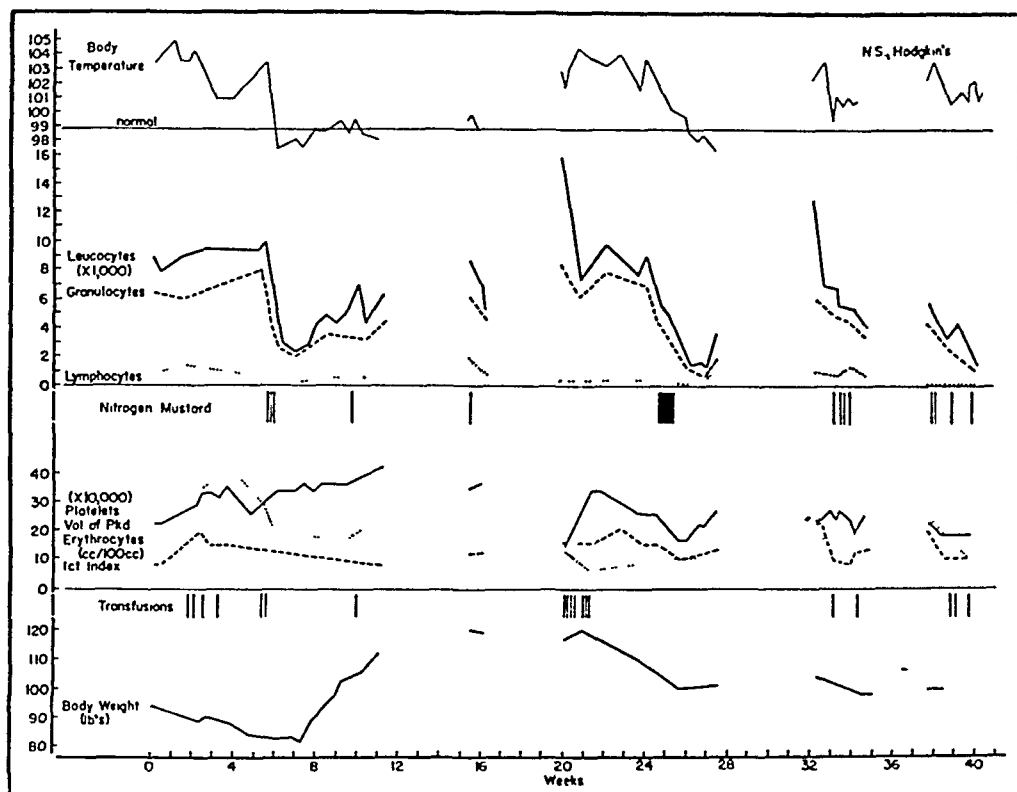


FIG. 1. Course of a patient with severe anemia somewhat hemolytic in type, associated with Hodgkin's disease who seemed in a terminal stage after treatment with roentgen irradiation and Fowler's solution. With blood transfusions as well as nitrogen mustard fever disappeared, the anemia was relieved and weight was gained. Several other remissions were produced in this patient but each was successively less striking and of shorter duration.

*Lymphosarcoma.* In this group of 11 cases great individual variation in response to nitrogen mustard therapy has been observed. The response has ranged from a remarkable melting away of tumor masses following treatment with long remission, to essentially no benefit whatever. In roentgen-ray resistant cases, no dramatic benefit has been observed like that seen in some cases of Hodgkin's disease.

*Leukemias.* Of the eight patients with *chronic myelocytic leukemia* treated with nitrogen mustard one was terminal on admission and resistant to roentgen-ray therapy. In this case nothing was achieved with nitrogen mustard therapy. Of the remaining seven patients good results have been obtained in three, fair results in one, and poor results in two, both of whom died after three months of therapy. One patient did not complete her

course of therapy. In several cases, it has been possible to produce remissions a number of different times by giving courses of three to five infusions of nitrogen mustard at two to four month intervals (figure 2). Where a favorable response to therapy has been achieved there has not only been a reduction in the white cell count to normal but the platelet count has returned to normal when it was above or below normal and anemia has been relieved. At the same time the spleen was greatly reduced in size, weight was gained, and a sense of well being returned. Thus the effect has been similar to that which is observed following roentgen-ray therapy. By giving two or three infusions on successive days at two to six week intervals it has been possible to maintain two patients in a satisfactory state of health.

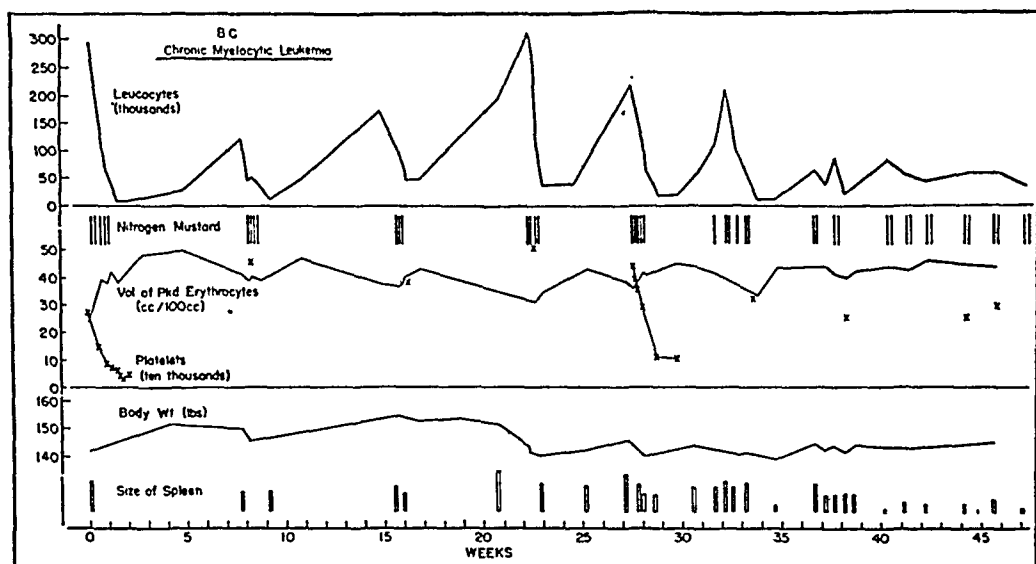


FIG. 2. Course of a case of chronic myelocytic leukemia under nitrogen mustard therapy. Note the drop in leukocyte count, disappearance of anemia, and gain in weight. This patient is now receiving treatment with two infusions of nitrogen mustard at intervals of two to four weeks as illustrated at the right-hand portion of the chart, and is responding very satisfactorily.

Of the 10 patients with *chronic lymphocytic leukemia* three patients are in remission nine to 26 months after therapy was first given. The cases of chronic lymphocytic leukemia seem to fall into one of two groups: (1) those patients who were really not ill and in whom the characteristic blood findings were more or less incidental; and (2) the cases of long standing with marked lymphadenopathy, splenomegaly, thrombocytopenia and severe anemia. The first group responded favorably to nitrogen mustard therapy and have had long remissions following treatment. The patients of the second group were refractory to the agent and responded not at all or only slightly after its administration (figure 3).

Eight patients with *acute or subacute forms of leukemia* have been treated and of these five must be classed as "poor" results and three as "fair" results. In two patients there was temporary improvement sufficient to enable the

patient to leave the hospital. In a third patient the acute course of the disease seemed to have been altered and at first there was some clinical improvement. Ultimately the patient failed to respond to further therapy, as was the case in all the rest. A gratifying result of treatment in two patients was the relief of severe bone pain which could be achieved even with extremely small doses of nitrogen (0.04 mg. per kg. body weight).

*Uncertain Diagnoses and Miscellaneous Disorders.* No alteration in the downward course of these patients was observed except possibly in two cases. One was a patient who had metastatic carcinoma of the mediastinal lymph nodes presumably from a uterine carcinoma. She suffered from chest pain and dyspnea and was temporarily relieved of these symptoms after nitrogen mustard therapy. Again, in a patient with metastatic anaplastic carcinoma of the chest wall and breast a remarkable regression of the metastatic nodules and reduction in jaundice followed nitrogen mustard therapy.

*Hematological Effects.* The most consistent effect of nitrogen mustard on the blood was a reduction in the total leukocyte count. This was reduced in all cases and the effect of the therapeutic agent was expressed not only in a fall in lymphocytes but also in granulocytes (figure 4). Varying with the magnitude of the initial white cell count, the level dropped to normal or leukopenic levels and in one patient dropped as low as 200 cells per cubic millimeter. Only in one case, however, did the clinical picture of agranulocytosis appear with sore throat and fever. The prompt administration of penicillin was effective in relieving the infection. In several instances the concurrent administration of this agent probably prevented the development of infection.

In general, the effect of nitrogen mustard on the blood was biphasic. There was frequently (1) an initial depression of leukocytes, and sometimes of platelets and red cells or a further drop from a previously existent low level, toward the end of the second week following therapy. Whether or not this occurred there was (2) a later therapeutic effect which corresponded usually with the degree of general improvement of the patient. The leukocyte count returned to normal, as did the platelets, and the anemia disappeared. This was noted not only in cases of chronic leukemia, as already mentioned, but was also seen in patients with Hodgkin's disease, some of whom had severe anemia prior to therapy. The length of time that the leukocyte count remained low following therapy depended to some extent on the severity of the leukopenia, but recovery usually began within a week.

There seemed to be no definite correlation in any of our cases between the degree of fall in red cell level and the size of the dose administered. It seemed that in the dosage used nitrogen mustard rarely produced anemia in cases of Hodgkin's disease and lymphosarcoma. An increase of anemia following therapy could as readily be attributed to the effect of the underlying disease as to the chemotherapeutic agent employed.

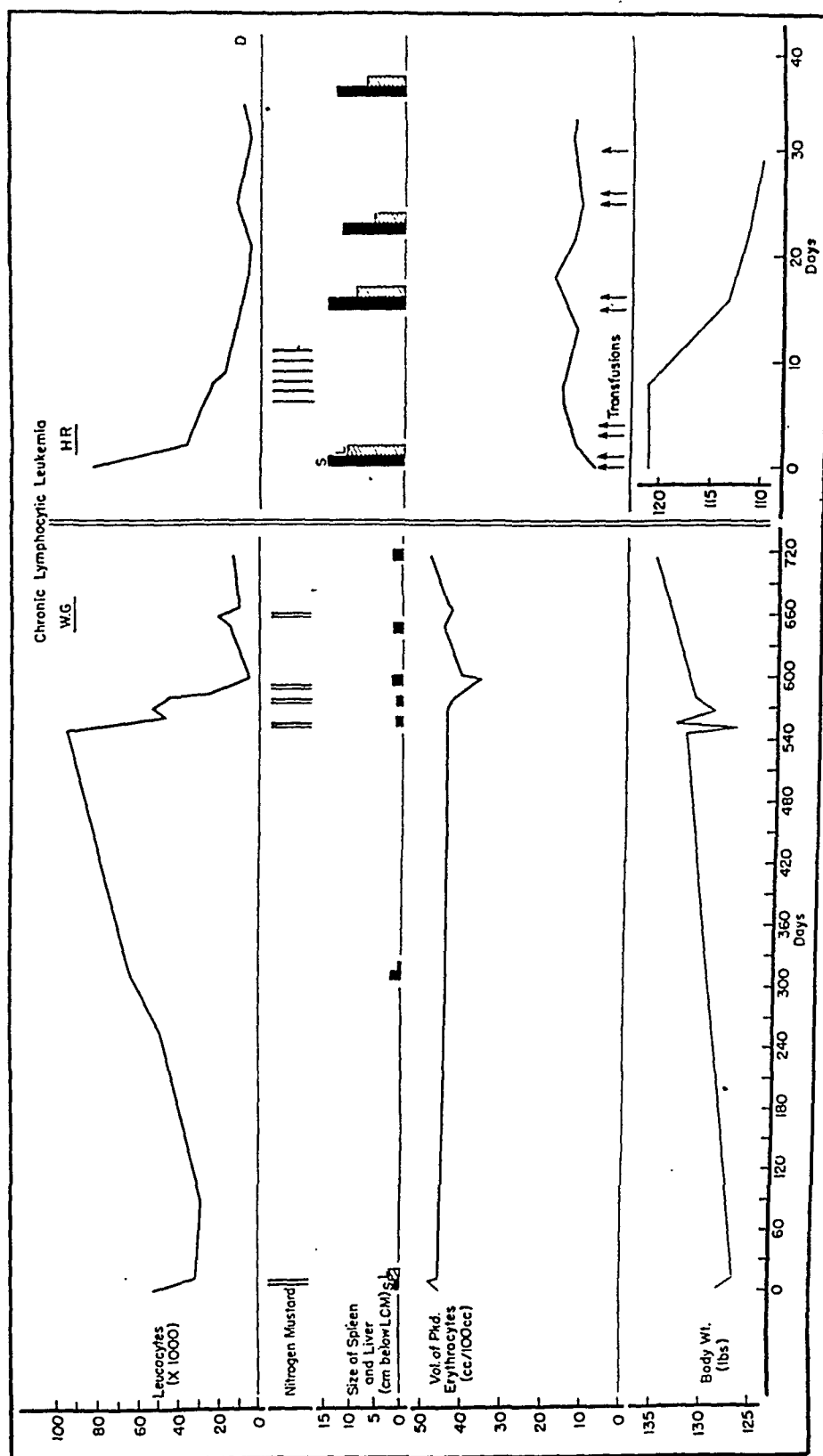


FIG. 3. Course of two cases of chronic lymphocytic leukemia under nitrogen mustard therapy. In W. G. (Case 1) the general condition was good from the beginning and only a slight increase in the sense of well-being was observed following therapy. In H. R. (Case 6) the general condition was poor and treatment produced no significant improvement.

Although thrombocytopenia was produced in a number of the patients (26 out of 77), petechiae appeared only in seven and, with the exception of one patient who died of lymphosarcoma, these cleared as the platelet count rose. There was never any serious bleeding in any of the cases.

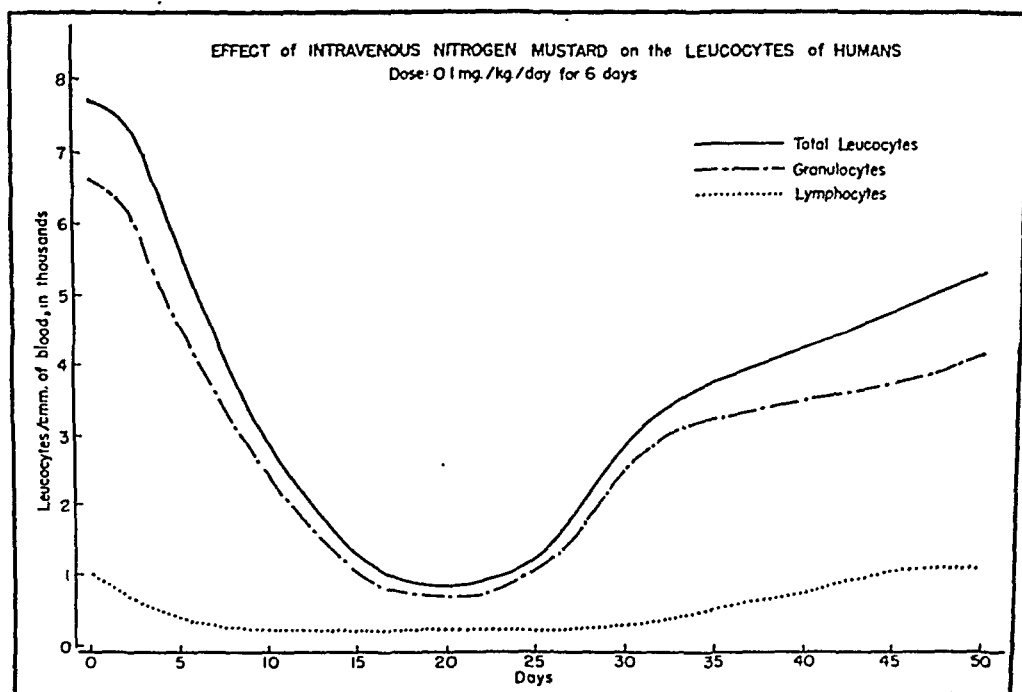


FIG. 4. Schematic diagram of effect of nitrogen mustard on the leukocytes.

*Toxic Effects.* Some degree of nausea and vomiting occurred in nearly every patient given nitrogen mustard. The gastrointestinal symptoms varied, however, from simple anorexia to severe nausea with repeated vomiting, in a few patients. These symptoms appeared within three hours after the injection of the drug and were of varying duration but rarely lasted more than a few hours. The first one or two infusions in a course of therapy usually produced more nausea than subsequent infusions. Many patients were relieved of the discomfort by preinfusion administration of a sedative. A satisfactory method of management is to give the patient a sedative in the early evening and to administer nitrogen mustard about 7:00 or 8:00 p.m. Thus, any nausea or vomiting which may be produced occurs at night and if the patient is sufficiently sedated he is not greatly disturbed. By this means food intake has not been interrupted to any great extent. A number of patients have expressed their preference for this time and mode of administration.

In only one patient was a significant degree of damage to the veins produced and this occurred prior to the introduction of the method of administration in the course of an intravenous saline infusion which has been



described already. Additional toxic effects which have been mentioned already are the severe leukopenia which can be produced by nitrogen mustard therapy and thrombocytopenia.

### DISCUSSION

An adequate evaluation of the usefulness of nitrogen mustard in the treatment of the conditions under discussion here would require the study of a much larger number of cases in each category, and observation for a longer period of time than has been possible so far. It seems clear, however, that nitrogen mustard therapy is comparable in its effect to that produced by adequate doses of roentgen therapy. Whether nitrogen mustard is more or less effective than roentgen therapy in Hodgkin's disease is difficult to state but one cannot help being impressed by the fact that in a number of patients who had apparently become resistant to roentgen therapy, substantial benefit followed the introduction of nitrogen mustard therapy.

There is no evidence from our cases that nitrogen mustard therapy possesses any advantage as compared with roentgen therapy in the treatment of lymphosarcoma.

A beneficial effect in cases of chronic myelocytic leukemia has been quite clear in a number of instances but again there is no evidence that this effect is greater than that achieved with roentgen therapy. The same can be said regarding chronic lymphocytic leukemia. The temporary remissions observed in two cases of acute leukemia and the relief of bone pain in this disease have been mentioned already.

Nitrogen mustard therapy offers the advantages of ease of administration and availability under conditions where roentgen therapy may not be obtainable. It must also be noted that the tolerance of patients with the disease under discussion to various therapeutic agents varies greatly. The availability of nitrogen mustard in addition to roentgen therapy offers another therapeutic tool. The effectiveness of nitrogen mustard in some cases of Hodgkin's disease which had become resistant to roentgen-ray therapy is a very important consideration. An important feature relating to the introduction of nitrogen mustards as therapeutic agents depends on the fact that the one employed in this study is but one of a series of compounds of almost infinite number. It can be hoped that, by changing substituent groups, the reactivity, toxicity and other important properties of the nitrogen mustards can be so altered that a much more valuable therapeutic agent than di( $\beta$ -chloroethyl) methyl amine hydrochloride can be discovered. The most important objection to nitrogen mustard is the fact that it is a potent hemopoietic toxin and that the margin of safety between the therapeutic dose and the serious toxic dose is narrow. Frequent careful hematologic examinations are, therefore, mandatory. In experienced hands, however, the agent is very useful and its use is associated with little danger.

Unfortunately, the response to nitrogen mustard in various patients seems to be largely unpredictable and consequently a therapeutic trial must, in the last analysis, give the answer as to whether this agent is likely to be beneficial or not.

### SUMMARY

1. The effects of di( $\beta$ -chloroethyl) methyl amine hydrochloride (nitrogen mustard) in 77 patients, 28 with Hodgkin's disease, 11 with lymphosarcoma, 26 with leukemia and 12 with miscellaneous disorders, are described.

2. A salutary effect upon lymph nodes, fever, splenomegaly and various clinical symptoms was observed in many patients with Hodgkin's disease, lymphosarcoma and leukemia.

3. In general, the effects of nitrogen mustard in these diseases were similar to those produced by roentgen irradiation.

4. Nitrogen mustard has produced remissions in several patients with Hodgkin's disease who were considered to be roentgen-ray resistant.

5. Toxic manifestations of nausea and vomiting were observed in most patients following nitrogen mustard administration but the intensity of these symptoms varied greatly and was almost insignificant in some.

6. Nitrogen mustard therapy almost invariably resulted in a decrease in leukocyte count with lymphocytopenia and granulocytopenia. This was often accompanied by a variable decrease in red cells and a decrease in platelets but in no patient did serious complications arise as a result of these effects.

7. Following the initial decrease in blood elements, an increase in red cells even with complete disappearance of anemia was the result in those patients responding favorably. Leukopenia and thrombocytopenia likewise disappeared.

8. Nitrogen mustard offers certain advantages as compared with roentgen irradiation in some cases of Hodgkin's disease and leukemia. These include the ease of administration, the effectiveness at times in patients "resistant" to roentgen-ray therapy and, very rarely, a better tolerance for nitrogen mustard than for irradiation. Ultimately, however, nitrogen mustard, like irradiation, has proved ineffective in many cases.

9. Adequate evaluation of the place of nitrogen mustard therapy in the management of "lymphomas" and leukemias must await a longer period of observation than has been possible so far and requires the study of a large number of cases. Experience to date, however, indicates that continued use is justified and a search for less toxic and more effective agents of this type is warranted.

## BIBLIOGRAPHY

1. GILMAN, A., and PHILIPS, F. S.: The biologic actions and therapeutic applications of the B-chloroethyl amines and sulphides, *Science*, 1946, ciii, 409.
2. GILMAN, A., GOODMAN, L., LINDSKOG, G. E., and DOUGHERTY, T.: 1942-43. (See GILMAN, A. and PHILIPS, F. S.<sup>1</sup>)
3. JACOBSON, L. O., SPURR, C. L., BARRON, E. S. G., SMITH, T., LUSHBAUGH, C., and DICK, G. F.: Nitrogen mustard therapy. Studies on the effect of methyl-bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 263.
4. WINTROBE, M. M., MCLENNAN, MARGARET T., and HUGULEY, C. M., JR.: Clinical experiences with nitrogen mustard therapy, *Tumor Symposium, Am. Assoc. Adv. Sci.*, 1947. (To be published.)
5. GOODMAN, L. S., WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A., and MCLENNAN, MARGARET T.: Nitrogen mustard therapy. Use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 126.

# THE DEVELOPMENT OF BASOPHILIC INCLUSION BODIES IN MYELOMA CELLS AFTER STILBAMIDINE TREATMENT\*

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It has been reported previously that in many cases of multiple myeloma injections of stilbamidine—occasionally of pentamidine—exert a favorable influence upon the excruciating pains from which the patients so frequently suffer.<sup>1, 2, 3, 4</sup> From the beginning it has been emphasized that the disease is not cured by stilbamidine. Even in patients who are markedly relieved, the characteristic myeloma cells still abound in the bone marrow, and Bence Jones proteinuria and hyperglobulinemia continue unabated. At the very best the disease may be halted temporarily. In some patients the relief of pains has persisted for many months. In many cases the pains recur after a shorter or longer period, but it is often possible by means of additional injections to bring relief anew. Nevertheless the death rate among these patients is still high. In patients with Bence Jones proteinuria and renal insufficiency the drug should be dispensed with caution.

It is well known that roentgen-ray treatment may occasionally alleviate the pain. Usually after one or more series of roentgen-ray treatments the disease becomes refractory. In several instances we have observed that after a series of stilbamidine injections such refractory cases could again be influenced favorably by roentgen-ray treatment.

TABLE I

Relation between the Development of Basophilic Inclusion Bodies in Myeloma Cells under Influence of Stilbamidine Treatment and the Signs of Abnormal Protein Metabolism

	Total Myeloma Patients Treated	Basophilic Inclusion Bodies Developed in
Hyperglobulinemia	13	12
Normal serum globulin $\bar{c}$ Bence Jones proteinuria	9	5
Normal serum globulin $\bar{s}$ Bence Jones proteinuria	10	0

It has been reported that after parenteral administration of stilbamidine basophilic cytoplasmic precipitates appear in the myeloma cells.<sup>5</sup> In the following article evidence will be presented which indicates that these characteristic precipitates are formed most readily in those patients whose protein metabolism shows the severest disturbances. Observations are now available on 32 patients with multiple myeloma treated with stilbamidine (table 1). Thirteen of these patients had an increase in the globulin content of the serum; in 12 the inclusion bodies developed readily. The thirteenth

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patient with hyperglobulinemia received stilbamidine injections only twice weekly, later three times weekly. Nine myeloma patients treated with stilbamidine had a normal serum globulin but showed marked Bence Jones proteinuria; in five of these patients basophilic inclusion bodies developed. Ten patients had neither increased globulin nor Bence Jones proteinuria. In none of these 10 patients could inclusion bodies be found, even after prolonged treatment.

TABLE II

Development of Basophilic Inclusion Bodies in Myeloma Cells under Influence of Stilbamidine  
Relationship with Globulin Content of the Serum

Name	Glob.	Formol gel	Bence Jones	Injections Daily		Injections Every Other Day		Total Dosage in Mg.	Inclusion Bodies
				Amt. Given in Mg.	Days	Amt. Given in Mg.	Days		
1. Hil.	9.8	++++	—	1300	10	—	—	1300	Positive
2. Low.	6.9	++++	—	1400	10	—	—	1400	Positive
3. Mor.	5.6	++++	+	2025	13	—	—	2025	Positive
4. Gersh.	3.0	++++	—	1975	16	—	—	1975	Positive
5. Robin.	4.2	++++	—	1350	8	1050	13	2400	Positive
I. Stern.	2.6	+	+	3150	23	—	—	3150	Positive
II. Zapet.	1.6	—	++	2100	19	—	—	2100	Positive
III. Bor.	1.5–3.2	— to +	++	600	7	1650	20	2250	Positive
IV. Ros.	2.2	—	++	2250	18	—	—	2250	Positive
V. Less.	*	—	+	—	—	—	—	—	Positive
VI. Stee.	1.6	—	++	2050	19	450	5	2500	Negative
VII. Eng.	2.1	—	++	1825	18	225	3	2050	Negative
VIII. Lipk.	2.2	—	++	3050	21	—	—	3050	Negative
IX. Perl.	1.4	—	—	1800	15	750	10	2550	Negative
X. Eis.	2.4	—	—	1350	8	2700	35	4050	Negative
XI. Kau.	2.5–3.2	—	—	2775	19	2250	45	5025	Negative
XII. Eps.	2.4	—	—	2700	17	1800	22	4500	Negative

\* Total protein 5.9%.

The treatment with stilbamidine in these 32 cases was not completely uniform. In some instances the drug was given daily, in others every second day. In most patients the injections were given intravenously. Bone marrow punctures were sometimes performed shortly after the beginning of treatment while in other patients several weeks elapsed before a bone marrow puncture was done. However, 17 of these 32 patients were treated with comparable daily doses of stilbamidine which were injected intravenously. Table 2 shows the results obtained in this group of 17 in whom the treatment was uniform. Five of these patients had a high serum globulin; in all five the daily intravenous injection of stilbamidine gave rise to the formation of inclusion bodies. In eight patients with normal serum globulin and Bence Jones proteinuria this happened five times. In four patients who had neither hyperglobulinemia nor Bence Jones proteinuria no basophilic inclusion bodies could be found. It follows from these figures that in patients with hyper-

globulinemia the basophilic inclusion bodies develop readily. This also occurs not infrequently in patients with a normal globulin content of the serum and with Bence Jones proteinuria. Up to the present time no basophilic inclusion bodies have been found after stilbamidine treatment of myeloma patients who had normal serum globulin and no Bence Jones proteinuria. It is interesting to note that all the patients who developed inclusion bodies although the globulin content of the serum was apparently normal, were treated intensively with daily injections. In myeloma patients who have hyperglobulinemia inclusion bodies are formed rapidly even when the stilbamidine treatment is not very intensive. Thus in myeloma patients with hyperglobulinemia, with or without Bence Jones proteinuria, basophilic precipitates develop regularly in the myeloma cells during stilbamidine treatment. This occurs much less readily in patients without hyperglobulinemia and then only if Bence Jones proteinuria exists.

It has been interesting to determine the minimum time and the minimum dosage of stilbamidine necessary for the development of basophilic inclusion bodies. In order to answer this question it seemed necessary to perform frequent bone marrow punctures. For obvious reasons this was difficult. The obstacle was circumvented in a patient with multiple myeloma and hyperglobulinemia in whose peripheral blood a small percentage of myeloma cells was present. In this patient after only eight injections of 150 mg. of stilbamidine fine basophilic granules could be detected in the myeloma cells of the peripheral blood. It is difficult to study this problem in routine blood smears which contain only 1 or 2 per cent of myeloma cells because, at least in the beginning of the treatment, only a small number of these rare cells show the presence of inclusion bodies. For this purpose the white cells of the peripheral blood were concentrated in the following way:

0.2 c.c. of an oxalate mixture consisting of 1.2 per cent of ammonium oxalate and 0.8 per cent potassium oxalate were evaporated in a centrifuge tube. Two c.c. of blood are added and centrifuged for three to five minutes at the speed of 2000. This supernatant serum is discarded and the sediment is transferred to a capillary tube. This capillary tube is centrifuged for three to five minutes at a speed of 2000. After centrifugation a clearcut separation between the red blood cells and the buffy coat is obtained. Then the capillary is broken off at a distance of about one millimeter above the buffy coat. The last remnant of the serum is sucked off with a fine capillary pipette. With the same fine capillary pipette the buffy coat is collected and smeared in the usual way on one or more glass slides.

The finding of basophilic inclusion bodies in the myeloma cells of the peripheral blood after the injection of 1200 milligrams of stilbamidine was confirmed by sternal punctures. In three other patients (Nos. 1, 2, and 3 of table 1) most of the myeloma cells of the bone marrow showed the

presence of basophilic inclusions after the injection of 1300, 1400, and 2025 milligrams of stilbamidine respectively.

Another point of interest is the question how long these inclusion bodies can persist after treatment has been stopped. It has become apparent that the inclusions can be found even if no stilbamidine has been given for many months. In one patient we observed that many of the myeloma cells still contained a considerable number of large inclusion bodies seven months after the injections had been terminated. In two other cases the interval between the last stilbamidine injection and the finding of inclusion bodies amounted to three and a half months and four months respectively.

### DISCUSSION

Since 1939 it has been known that stilbamidine has a specific curative influence in kala azar. Stilbamidine was tried in multiple myeloma because the two diseases had one characteristic in common: both in kala azar and in multiple myeloma an increase of the globulin content of the blood serum occurs frequently. In advanced cases of kala azar this increase is found almost constantly; in multiple myeloma hyperglobulinemia occurs in only about 60 per cent of the cases.

The results reported in this article indicate that a connection apparently exists between the abnormal protein metabolism found in multiple myeloma (hyperglobulinemia, Bence Jones proteinuria) and the formation of characteristic basophilic inclusion bodies in the myeloma cells under the influence of stilbamidine. Histochemical analysis has demonstrated that these basophilic inclusion bodies contain a conjugation product of ribose nucleic acid<sup>6</sup> and stilbamidine.<sup>7</sup> The ribose nucleic acid is a derivative of the cytoplasmic nucleoproteins. The latter nucleoproteins consist of ribose nucleic acid conjugated with a protein, the character of which is still unknown. When stilbamidine is brought into contact with nucleoprotein in vitro, a conjugation product of stilbamidine and ribose nucleic acid precipitates out.<sup>8</sup> At the same time the protein component of the nucleoprotein is liberated and goes into solution. Histochemical investigation of the basophilic inclusion bodies which appear in myeloma cells after stilbamidine injections indicate that a comparable process takes place in the cytoplasm of the myeloma cells. Stilbamidine evidently reacts in vivo with the cytoplasmic nucleoproteins of the myeloma cells. This reaction leads to the formation of a conjugation product of stilbamidine and ribose nucleic acid which is visualized in the form of basophilic inclusion bodies.

Autopsies have shown that these basophilic precipitates develop exclusively in the myeloma cells and in no other marrow cells. It is therefore highly probable that stilbamidine combines much more readily with the cytoplasmic nucleoproteins of the myeloma cells than with the nucleoproteins of other cells. Certain arguments can be brought forward in favor of the contention that the cytoplasmic proteins of the myeloma cells differ significantly

from the cytoplasmic nucleoproteins of other body cells. The cytoplasmic nucleoproteins of cells play an important rôle in the protein synthesis which takes place in the cells.

Many authors have emphasized that all cells with a high concentration of cytoplasmic nucleoproteins are characterized by intense protein synthesis. This holds true for the pancreatic cells which secrete protein and for the liver cells which synthesize plasma proteins. It also holds true for cells which need protein because they multiply rapidly, such as tumor cells, cells of the basal layer of the skin, and organisms such as viruses, yeasts and bacteria.<sup>9</sup> The high content of nucleoprotein found in the cytoplasm of the myeloma cells has also been considered as an indication of a rapid production of globulins and of Bence Jones proteins in these cells.<sup>10</sup> Lately it has been reported that the character of the proteins manufactured by the cell depends upon the character of its cytoplasmic nucleoproteins.<sup>11</sup> The latter finding leads to the conclusion that the more the cytoplasmic nucleoproteins of certain body cells differ from the norm, the more the protein synthesis of these special cells will differ from those in the other cells. The reverse must obviously be true also. In a cell like the myeloma cell which produces abnormal proteins (abnormal globulins and Bence Jones protein) cytoplasmic nucleoproteins must be present which differ from the nucleoproteins of all other normal and abnormal body cells. This may well explain why the nucleoproteins of myeloma cells show reactions which other nucleoproteins do not show and also why stilbamidine forms visible conjugation products with the cytoplasmic nucleoproteins of the myeloma cells but not with nucleoproteins of other cells.

It is interesting to note that the formation of the inclusion bodies is more marked in those myeloma patients who have hyperglobulinemia than in those who do not. It seems reasonable to suppose that in myeloma patients who have hyperglobulinemia or Bence Jones proteinuria the protein metabolism of the myeloma cells will be more abnormal than in myeloma patients with normal serum globulins and without Bence Jones proteinuria. In the former patients more abnormal nucleoproteins will be present. Under these circumstances stilbamidine evidently replaces the protein component of the cytoplasmic nucleoproteins, and thereby leads to the formation of basophilic inclusion bodies. This could also explain why no inclusion bodies in myeloma cells have been observed after stilbamidine treatment of patients in whom the change of the protein metabolism was less apparent, that is, in myeloma patients without hyperglobulinemia and without Bence Jones proteinuria.

It is perhaps unnecessary to mention that determinations of the globulins of the blood by the Howe technic (precipitation with different concentrations of sodium sulfate solutions) give only a superficial impression of the abnormalities in the globulin metabolism of the myeloma patient. The same holds true for various qualitative tests such as the formol gel test. A good example of the inadequacies of these tests is given by patient No. 1 of table 2.



The globulin content of this patient was determined repeatedly and was found to be only 2.6 per cent. The formol gel test was either negative or weakly positive on several occasions. Nevertheless, the serum of this patient must contain either an abnormal globulin or a normal globulin fraction in abnormal quantities as shown by the Sia globulin test.<sup>9</sup> Dilution of 0.02 c.c. of blood with 0.6 c.c. of distilled water immediately gave rise to a heavy flocculation, indicating that an abnormal globulin must have been present. This patient, as a matter of fact, developed many granules in the myeloma cells after stilbamidine treatment.

### SUMMARY

After daily intravenous injections of 150 mg. of stilbamidine basophilic precipitates developed in the myeloma cells of 12 of 13 patients who had hyperglobulinemia. Patients with multiple myeloma whose serum globulin content was normal showed much less tendency to develop these precipitates. As a matter of fact, the formation of these inclusion bodies could be observed in only five of nine myeloma patients with a normal globulin content of the serum and with Bence Jones proteinuria. In 10 patients without hyperglobulinemia and without Bence Jones proteinuria intravenous injections of stilbamidine did not result in the development of inclusion bodies.

Inclusion bodies developed after as few as seven to 10 daily intravenous injections of 150 mg. of stilbamidine had been given.

After cessation of the stilbamidine treatment the inclusion bodies persisted for many months.

### BIBLIOGRAPHY

1. SNAPPER, I.: Influence of stilbamidine on multiple myeloma, *Jr. Mt. Sinai Hosp.*, 1946, xiii, 119-127.
2. SNAPPER, I.: Influence of stilbamidine and pentamidine on the course of multiple myeloma, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 157-161.
3. BAUER, W., and JACOBSON, B.: Cases from the Medical Grand Rounds of the Massachusetts General Hospital, *Am. Pract.*, 1947, i, 379.
4. REICH, C., and BRODSKY, A.: Coexisting multiple myeloma and Paget's disease of bone treated with stilbamidine, *Jr. Bone and Joint Surg.* (in press).
5. SNAPPER, I., and SCHNEID, B.: The influence of stilbamidine on myeloma cells, *Blood*, 1946, i, 534-536.
6. SNAPPER, I., MIRSKY, A., RIS, H., SCHNEID, B., and ROSENTHAL, M.: Development of inclusion bodies containing ribonucleic acid in myeloma cells after injections of stilbamidine. Determination of stilbamidine in myeloma tissue, *Blood* (in press).
7. SNAPPER, I. and Associates: Unpublished results.
8. KOPAC, M.: Cellular mechanisms in chemotherapy, *Trans. New York Acad. Sci.*, 1945, viii, 5-10.  
KOPAC, M.: Dissociation of protamine nucleates by aromatic diamidines, *Cancer Res. (Proc.)*, 1946, vi, 491.
9. DAVIDSON, J. N.: Nucleoproteins in growth and development, *Edinb. Med. Jr.*, 1945, lii, 344-356.

10. BJORNEBOE, M., and GORMSEN, H.: Experimental studies on the rôle of plasma cells as antibody producers, *Acta path. Scand.*, 1943, xx, 649.  
THORELL, B., and WISING, P.: Om äggvitebildningen i myelomcellen, *Nordisk Medicin*, 1944, xxiv, 1842-1846.  
BING, J., FAGRAEUS, A., and THORELL, B.: Studies on nucleic acid metabolism in plasma cells, *Acta physiol. Scand.*, 1945, x, 282-294.
11. DEMPSEY, E. W., and WISLOCKI, G. B.: Histochemical contributions to physiology, *Physiol. Rev.*, 1946, xxvi, 1-27.
12. SNAPPER, I.: *Chinese Lessons to Western Medicine*, 1941, Interscience Publishers, Inc., New York, p. 106.

# NEW DRUGS OF VALUE IN THE TREATMENT OF EPILEPSY \*

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A DRUG that is good for one type of epileptic seizure may be bad for another; for example, Dilantin is an excellent anticonvulsant, but in many cases it increases the number and severity of petit mal seizures, and Tridione, which is often dramatically effective against petit mal, may increase the number of grand mal. Thus, in order to proceed as rationally as possible with the treatment of an epileptic patient, the type or types of epileptic seizure should be classified. The major types of epileptic seizure and the drugs which are beneficial in their treatment are shown in table 1. This table also indicates the clinical manifestations and types of electrical discharges which characterize the major types of epileptic seizure. A more detailed description of the clinical and electroencephalographic characteristics of various types of seizure is included under corresponding paragraph headings later in this article.

Classification of seizures is based on the clinical history and the electroencephalographic findings. The electroencephalogram is not absolutely essential but in most cases it makes the selection of medication easier and the results more consistent. However, even if the type or types of seizure cannot be classified, the case should be treated. The number of drugs to be tried is not great and a satisfactory result can be attained by trial and error.

The general principle of medication is as follows: Start with the drug which is presumed to be most effective. The dose should be increased to tolerance or to a level at which seizures are prevented. If the first drug reduces the number of seizures but does not prevent them the dosage should be adjusted so that no more than tolerable side effects are produced, and with this as a maintenance dose the next most promising remedy should be added. The dose of the supplementing drug should be raised to tolerance or until seizures are controlled. This procedure should be repeated with each drug in turn until seizures have been controlled or until all drugs have been tried at maximal tolerated dosage. Any drug which produces no definite benefit should, of course, be omitted, but before discarding a drug the dosage should be raised to the maximum that is tolerated. The mistake most commonly made in the treatment of epilepsy is *under-medication*, because the physician has assumed some arbitrary limit on dosage.

\* Read before the General Assembly of the Illinois State Medical Society May 14, 1947. From the University of Illinois, College of Medicine, Department of Psychiatry, Chicago, Illinois.

TABLE I  
Guide to Medical Treatment of Epilepsy

Type of Epilepsy	Clinical	Age	E.E.G.	Medication	Average Adult Dose†	Limiting Side Effects	Signs of Sensitivity
Grand Mal	Convulsions	Any	Slow or fast spikes and petit mal variant. (Rarely grand mal discharges)	{ Dilantin	1½ grs. t.i.d. after meals. Usual maximum 6 grs./day	Diplopia Staggering (May increase petit mal)	Overgrowth of gums Overgrowth of body hair Itching rash on extremities Gastric irritation
Focal	Focal convulsions	Any	Focal spikes or Focal slow waves	{ Phenobarbital Mesantoin	1½ grs. h.s. Usual maximum 3 grs./day 1½ grs. t.i.d. Usual maximum 6 grs./day	Sleepiness Sleepiness	Scarlatiniform rash* Fever Lymphadenopathy
Petit Mal (Psychomotor Epilepsy)	Frequent short lapses of consciousness. Blinking, head nodding.	Usually children	3 per second wave-and-spike	{ Bromides Tridione with monthly white count	18 grs. sodium bromide t.i.d. (Blood bromide 150-300 mg. per 100 c.c. of blood) 4½ grs. t.i.d. or until seizures are controlled	Inability to see in a bright light Drowsiness	Acne Depression and confusion Hiccoughs Acneiform rash Leukopenia*
Myoclonic	Lightning-like jerks	Usually children	3 per second wave-and-spike	{ Mebaral Ketogenic diet	6 grains	Sleepiness	Loss of weight
Psychomotor	Periods of confusion with incoordination and apparently purposeful movements	Usually adults	Positive spikes. Negative spike focus in temporal lobe with spread to anterior-inferior part of head.	Any and all anti-epileptic substances. (Medical treatment, generally unsatisfactory.)			

\* These signs of sensitivity require omission of responsible drug.

† Dose should be raised until seizures are controlled or until limiting side effects or signs of sensitivity develop.

## TONIC-CLONIC CONVULSIONS

True convulsions, whether short or long in duration, whether generalized or focal in distribution, respond best to Dilantin, phenobarbital and Mesantoin.

*Dilantin.* Dilantin<sup>1</sup> has its chief use in the treatment of *grand mal* epilepsy, and any type of true convulsion. The general rule of raising the dose to tolerance, or until seizures are controlled, should be followed. Infants can usually tolerate 3 grains per day; children 4.5 grains, and adults 6 grains per day. It should be remembered that these dosages are intended merely as rough approximations.

The most usual side effects from Dilantin are dizziness, staggering and double vision. This substance is somewhat irritating to the gastric mucosa and should be taken after meals. Side effects which are encountered rather infrequently and therefore classified as sensitivities are the following: Overgrowth of the gums, overgrowth of body hair, and an itching rash, chiefly on legs and arms. All these disappear promptly on reducing the dosage or ceasing Dilantin medication.

Dilantin may increase petit mal disorder; this limits its value in certain cases. It is sometimes effective against psychomotor disorders.

*Phenobarbital.* Phenobarbital<sup>2</sup> has its chief use in the treatment of grand mal seizures and true convulsions of all types. It is usually most effective as a supplement to Dilantin. It is not ordinarily effective against petit mal. Though worth trying in cases with psychomotor seizures, in some cases it increases the frequency of the attacks. The usual and almost the only limiting side effect is excessive drowsiness, but since over-sedation is commonly misinterpreted by teachers and employers as mental retardation it cannot be dismissed as a minor complication. Unless other means of controlling seizures fail, the dose of phenobarbital should be kept below that which produces hypersomnia. The sleep-producing effect of this drug is least disturbing if it is given in a single dose an hour before bedtime. There is a wide range of tolerance, but commonly effective daily doses are:  $\frac{3}{4}$  grain for infants, 1 grain for children, and  $1\frac{1}{2}$  grains for adults. As stated before, however, if control of seizures is not obtained on low dosage the level should be raised to tolerance.

*Mesantoin.* In cases of grand mal epilepsy, where Dilantin and phenobarbital are unable to prevent seizures or where the dose necessary to control seizures produced undesirable side effects, Mesantoin<sup>3,4</sup> should be tried. One person in 10 is sensitive to this substance and for that reason it is ordinarily reserved until after phenobarbital and Dilantin have been tried. Sensitivity is indicated by a scarlatiniform rash, swollen lymph glands in the scalp and in the neck, and by fever. The patient should be warned to be on guard against such a reaction. If it occurs the Mesantoin should be discontinued promptly; thereafter the entire reaction will subside within two to

four days. A sensitive patient may be desensitized by giving Mesantoin in small, gradually increasing dosage, starting with approximately  $\frac{1}{2}$  of a grain ( $\frac{1}{4}$  of a tablet) per day and increasing the dose by  $\frac{1}{2}$  of a grain per day each week.

The usual limiting side effect encountered with Mesantoin medication is hypersomnia; therefore, it is used more advantageously in combination with Dilantin than with phenobarbital. In ordinary cases medication should be started with a dose of  $1\frac{1}{2}$  grains per day ( $\frac{3}{4}$  of a grain in young children) while the patient is maintained on whatever Dilantin and phenobarbital dosage has been found most effective and tolerable. In the second week the dose can be raised to 3 grains per day, and in the third week to  $4\frac{1}{2}$  grains per day. Most patients become drowsy on dosages of about  $4\frac{1}{2}$  grains, but the dosage should not be limited until hypersomnia develops or until seizures cease. As the Mesantoin dosage is elevated to a level producing hypersomnia the phenobarbital should be reduced.

*Bromides.* Bromides<sup>5</sup> are of limited value because their anti-convulsant action is feeble and the toxic or sedative dose is close to or identical with the anti-convulsant dose in the great majority of cases. However, if seizures cannot be controlled with other drugs recourse should be had to bromides either alone or in combination with other substances. The salt intake should be kept low and maintained as nearly constant as possible. Attempts to avoid bromide acne by the administration of iodides are irrational because such procedures are equivalent to reducing the bromide dosage; the iodides merely displace the bromides in the body.

#### PETIT MAL SEIZURES AND MYOCLONIC JERKING

The term petit mal is now used in a restricted sense to apply to a type of brief and relatively mild seizure that is most common in children. There is no tonic component. The patient stares, blinks rhythmically with an approximately three-per-second rhythm, and nods his head. Sometimes the arms are involved, or the trunk; rarely the legs. Posture is usually maintained, but consciousness is impaired or lost. The attacks usually last only a few seconds and occur many times a day. This is a general description of the petit mal seizure; any of the above features may be omitted and the patient may just stare. The finding that clinches the diagnosis is the characteristic three-per-second wave-and-spike pattern in the electroencephalogram.

Seizures of the petit mal type have been referred to as pyknoleptic seizures. When they are the only type of seizure present the case was formerly diagnosed as *pyknolepsy*; however, in view of the identity of the pathological physiology in pyknolepsy and petit mal epilepsy a separate diagnostic category does not seem necessary.

Myoclonic jerking is common in epilepsy and it is often based upon the same type of disorder as the petit mal seizure, i.e., three-per-second wave-and-spike.

*Tridione.* In general, the best medication for petit mal seizures and myoclonic jerking is Tridione.<sup>6, 7</sup> The dosage can be started at  $4\frac{1}{2}$  grains per day, and raised by  $4\frac{1}{2}$  grains each day until seizures cease, or until limiting side effects develop. However, where seizures are not occurring every day the interval between increases in dosage should be lengthened. The ordinary limiting side effects are day blindness, usually reported by the patient as photophobia or inability to see in a bright light (hemeralopia), and drowsiness. On higher dosage attacks of hiccoughing are common. These symptoms are not serious; they disappear promptly on reducing the dosage. Once seizures are controlled the patient can often be maintained on a lower dosage than that which was necessary to stop the attacks in the first place; therefore, it is in some cases desirable to raise the dosage to a high level where seizures are prevented, hold it at this level for several days in spite of toxic side effects, and gradually decrease the dosage thereafter. Many patients can be maintained seizure-free on two to four capsules per day ( $4\frac{1}{2}$  grains in a capsule), but in some cases it is necessary to use a maintenance dose of 6 to 8 capsules per day and "shock treatment" with doses as high as 12 capsules per day may be necessary to stop the seizures. However, every effort should be made to drop the dosage, and a high level should be maintained only when it is found that seizures recur on lower dosage.

Fatal cases of leukopenia resulting from Tridione medication have been reported,<sup>8, 9</sup> but experience indicates that this drug can be used safely if a white-cell count and platelet estimation are obtained every month.<sup>10</sup> A great reduction in platelets or a white-cell count below 3000 are indications for discontinuation of Tridione therapy.

Tridione may make grand mal seizures occur more frequently. If no grand mal seizures have been reported and a subclinical grand mal component is present, the institution of Tridione medication may precipitate the first grand mal attack. In the presence of clinical grand mal, or of an electroencephalogram suggesting a grand mal component, phenobarbital or Mebaral should be used in addition to Tridione. Dilantin may be used to prevent grand mal seizures when these are found in association with petit mal, but Dilantin commonly increases petit mal disorder.

*Ketogenic Diet.* A diet in which sugar and starches are interdicted and in which nourishment is obtained chiefly from proteins and fats produces an altered body metabolism that is often beneficial in petit mal and myoclonic epilepsy.<sup>11</sup> Such a diet is expensive, difficult to maintain, sometimes distasteful and always troublesome. It is rarely effective in children over the age of ten. Such a diet may control seizures when Tridione does not and,

in cases where Tridione has given partial control, it may be used to supplement Tridione medication.

*Mebaral.* As a supplement to Tridione and also to reduce the possibility or likelihood of grand mal, Mebaral is of value. The dosage is double that of phenobarbital.

### PSYCHOMOTOR SEIZURES

In a psychomotor seizure the patient seems to be acting out a bad dream. Movements are more or less purposeful, though usually poorly coördinated. Such attacks have been referred to as epileptic equivalents. They are commoner in middle-aged persons than in children. Personality disorders are a frequent accompaniment.

Unfortunately, none of the substances that are useful against other types of seizures are generally effective against psychomotor attacks, and there is at present no known drug which by any stretch of the imagination can be called specific against psychomotor epilepsy. However, all remedies should be tried, and in rare cases a brilliant therapeutic result will be attained. Mesantoin should certainly be tried alone or in combination with other substances if seizures are not controlled with phenobarbital, Dilantin or Tridione. In some cases psychomotor attacks are precipitated by phenobarbital; more rarely by Dilantin.

### MIXED CASES

It should not be assumed that the presence of one type of seizure excludes others. Mixed seizure and cases with more than one type are common. Petit mal attacks tend to disappear in early adult life, but sometimes they are replaced by grand mal. Grand mal attacks also tend to decrease and become less severe with increasing age, but grand mal may be replaced by psychomotor seizures. The prognosis is brightest for cases with petit mal seizures only; next, for those with grand mal, particularly the idiopathic type, and it is worst for cases with psychomotor seizures, chiefly because specific medication is lacking. Where all three types of seizure are found together the prognosis is exceedingly bad.

### GENERAL CONSIDERATIONS REGARDING MEDICATION

Regardless of the type of seizure no case should be abandoned or allowed to continue having seizures without full trial of all anticonvulsants at maximal tolerated dosage. Since seizures and their causes are diverse a variety of remedies will probably always be necessary. The distinction between idiopathic and symptomatic epilepsy is generally valid and the drugs at present available for the treatment of epilepsy are more effective against idiopathic than against symptomatic epilepsy.



The informed practitioner will be able to treat successfully 75 per cent of patients with seizures. The remaining 25 per cent will be especially resistant cases, many with severe brain damage or additional complications. Such cases should be given access to the most advanced and expert treatment by referring them to qualified specialists. The task of the specialist will be greatly simplified if all generally available anti-convulsant substances have previously been given an adequate trial by the referring physician.

### CONCLUSION

Since epilepsy is a common and important disorder which usually responds to medicinal treatment, physicians should be aware of the clinical and electroencephalographic features of the major types of seizure and should be able to apply with discrimination the six or seven remedies that are now of recognized value.

### BIBLIOGRAPHY

1. MERRITT, H. H., and PUTNAM, T. J.: Sodium diphenyl hydantoinate in the treatment of convulsive disorders, *Jr. Am. Med. Assoc.*, 1938, cxi, 1068.
2. HAUPTMANN, A.: Luminal bei Epilepsie, *Munchen. med. Wchnschr.*, 1912, ii, 1907.
3. LOSCALZO, A. E.: Treatment of epileptic patients with a combination of 3-methyl 5, 5 phenylethyl-hydantoin and phenobarbital, *Jr. Nerv. and Ment. Dis.*, 1945, ci, 537.
4. KOZOL, H. L.: The treatment of epilepsy with methylphenylethyl hydantoin (Mesantoin), *Proc. Assoc. Res. Nerv. and Ment. Dis.*, 1946. In press.
5. LOCOCK, C., in discussion on SIEVEKING, E. H.: Analysis of 52 cases of epilepsy observed by the author, *Lancet*, 1857, i, 528.
6. PERLSTEIN, M. A., and ANDELMAN, M. B.: Tridione—its use in convulsive and related disorders, *Jr. Pediat.*, 1946, xxix, 20.
7. LENNOX, W. G.: Petit mal epilepsies. Their treatment with Tridione, *Jr. Am. Med. Assoc.*, 1945, cxxix, 1069.
8. MACKAY, R. P., and GOTTSTEIN, W. K.: Aplastic anemia and agranulocytosis following Tridione, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 13-16.
9. HARRISON, F. F., JOHNSON, R. D., and AYER, D.: Fatal aplastic anemia following use of Tridione and Hydantoin, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 11-13.
10. LENNOX, W. G., and DAVIS, J. P.: Effects of trimethyloxazolidine dione (Tridione) and of dimethylethyloxazolidine dione on seizures and on the blood, *Proc. Assoc. Res. Nerv. and Ment. Dis.*, 1946. In press.
11. PETERMAN, M. G.: The ketogenic diet, *Jr. Am. Med. Assoc.*, 1928, xc, 1427.

# INSULIN RESISTANCE \*

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It is well known that marked variations in sensitivity to insulin are found among diabetics, even in the absence of complications. This has led to attempts at classification into one of three categories, namely: (a) insulin sensitive, (b) insensitive, and (c) resistant. Insulin resistance is rare but is readily distinguished from the other two categories. According to the definition of Martin, Martin, Lyster and Strouse,<sup>1</sup> insulin resistance is present when doses of 200 units or more per day fail to reduce the blood sugar in non-acidotic patients during 48 hours' observation. This was based upon Root's calculation that depancreatized man should require 200 to 300 units of insulin daily. Although more recent observations<sup>2,3</sup> have indicated that a completely depancreatized man is sensitive to insulin and requires only from 35 to 50 units daily rather than the calculated 200 to 300 units, the criteria of Martin et al. are nevertheless useful in defining the rare case of insulin resistance from the case of insulin insensitivity.

Since it has been shown that human diabetes resulting from complete pancreatectomy can be controlled on 35 to 50 units daily, insulin requirements in excess of 200 units daily cannot be ascribed exclusively to destructive lesions of the pancreas. A classification of the reported causes of insulin resistance is presented in table 1.

TABLE I  
Classification of Causes of Insulin Resistance

- A. Unavailability of administered insulin due to
  - 1. Failure of absorption
  - 2. Excessively rapid excretion
 } A possibility which has been excluded in reported cases<sup>4, 5, 6</sup>
- B. Neutralization or destruction in blood or tissues
  - 1. Abnormal leukocytic activity
    - (a) Pyogenic infection with leukocytosis<sup>7</sup>
    - (b) Eosinophilia<sup>8</sup>
    - (c) Leukemia<sup>9</sup>
  - 2. Excessive output of hormonal antagonists<sup>10</sup>
    - (a) Anterior pituitary and/or adrenal cortex<sup>11, 12</sup>
      - 1. Cushing's syndrome<sup>13</sup>
      - 2. Acromegaly<sup>14</sup>
    - (b) Hypothalamus and posterior pituitary<sup>15, 16, 17, 18</sup>
    - (c) Thyroid<sup>19, 20</sup>
  - 3. Development of antibodies
    - (a) Accompanying signs of allergy to insulin-neutralizing antibodies demonstrated<sup>21, 22, 23, 24</sup>
    - (b) Allergy present but no insulin-neutralizing antibodies demonstrated<sup>1, 5, 25, 26, 27</sup>

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- (c) Neutralizing antibodies demonstrated but no accompanying signs of allergy <sup>28, 29, 30, 31, 32, 33</sup>
- C. Inability of end organs to utilize insulin
  - 1. Acidosis and/or infection <sup>8, 30, 34, 35, 36, 37, 38</sup>
  - 2. Diffuse hepatic disease with defective glycogen storage and/or excessive gluconeogenesis
    - (a) Hemochromatosis <sup>39, 40, 41</sup>
    - (b) Acute and chronic hepatic degeneration <sup>42, 43, 44, 45</sup>
- D. Unknown <sup>4, 46, 47, 48, 49, 50, 51</sup>

Thus insulin resistance has occurred under conditions which might facilitate destruction of insulin in the blood or tissues, such as in (1) states associated with abnormal leukocytic activity, e.g. leukocytosis, eosinophilia, leukemia; (2) in endocrine diseases accompanied by an excessive output of hormonal antagonists; and (3) in allergic states associated with the development of insulin neutralizing antibodies. Insulin resistance has also been reported under conditions which might interfere with ability of end organs to utilize insulin as in acidosis, infection or diffuse hepatic disease with defective glycogen storage.

Cases are encountered where no recognizable cause of insulin resistance can be found despite careful study. During the past three years we have had three such cases under observation which showed spontaneous appearance and disappearance of insulin resistance. These cases form the subject of this communication.

*Case 1 (Chart 1).* N. E., a 60 year old colored female, was first admitted on June 15, 1943. She had been in fairly good health until January, 1942 when polydipsia, polyuria, polyphagia and generalized pruritus set in. By April her weight had dropped from 160 to 130 pounds, and at that time she was hospitalized elsewhere. She was regulated on a diet with 40 units of protamine zinc insulin and 20 units of regular insulin daily, which was gradually reduced to a mere 10 units of protamine zinc insulin daily by June, 1942. Her weight at that time was 135 pounds. In July she stopped taking insulin against medical advice and in August, because of the recurrence of symptoms, she was again admitted to another hospital. The diabetes was well controlled on a diet of protein 75 grams, fat 70 grams, carbohydrates 200 grams and 40 units protamine zinc insulin daily. Her weight rose to 140 pounds. A few weeks after discharge she again discontinued her insulin injections, but she remained in good health until April, 1943 when the symptoms of diabetes mellitus were noticed again. On her own initiative she resumed taking protamine zinc insulin 40 units daily and symptoms disappeared rapidly. With the alleviation of her symptoms, she again discontinued her insulin injections; however, polydipsia, polyuria, polyphagia and pruritus recurred, leading to admission to the City of Detroit Receiving Hospital on June 15, 1943.

Past history: She had received two intramuscular injections for syphilis in 1927 and four intravenous injections in 1939. She had had three pregnancies, all of which ended in miscarriages. Her menstrual history was normal up until the age of 50 when she passed through a normal menopause. In 1923 she was told that she had a uterine fibroid. Allergic history was entirely negative. One sister, age 80, had mild diabetes. Family history was otherwise irrelevant.

Physical examination revealed an undernourished colored female, who exhibited evidence of generalized pruritus. Blood pressure 100 mg. Hg systolic and 70 diastolic, temperature 98.6, pulse 80. The pupils were equal and regular and reacted well to

accommodation but sluggishly to light. Ocular fundi revealed Grade I arteriosclerosis. There was no diabetic retinopathy. There were early lenticular cataracts. Visual fields were normal. The pharynx, teeth and tongue were negative. There was moderate non-specific anterior cervical lymphadenopathy. A small adenoma of the left lobe of the thyroid was palpated. There were no signs of hyperthyroidism. The heart and lungs were normal. The liver and spleen were not palpable. There was no abdominal tenderness. On bimanual examination the pelvis was found to be filled with a large nodular, non-tender mass extending up to the umbilicus. The patellar and tendon Achilles reflexes were absent bilaterally. The sense of motion and position, vibratory sense and pain sense were unimpaired. The impression on admission was (1) diabetes mellitus, uncontrolled, (2) uterine fibromyoma.

Laboratory data: hemoglobin 11.5 gm.; WBC 5,750, 50 per cent neutrophils, 42 per cent lymphocytes; 7 per cent monocytes, 1 per cent eosinophiles. Subsequent blood counts showed no significant variation. Repeated examinations of the urinary sediment were normal. Stool examinations were negative for undigested fat and meat fibers. Blood diastase was 93 units. Blood urea 20 mg. per 100 c.c. Urea clearance 95 per cent. Plasma cholesterol 364 mg. per 100 c.c. Serum calcium 9.8 mg. and phosphorus 3.6 mg. per 100 c.c. Bromsulphthalein test using 5 mg. per kg. was normal. Hippuric acid test showed 1.87 gm. benzoic acid excretion. Urinary urobilinogen was slightly abnormal on one occasion, but normal thereafter. On August 25, 1943 the serum albumin was 2.9 gm., globulin 2.0 gm. per 100 c.c.; on October 9, 1943 the serum albumin was 3.6 gm., globulin 2.8 gm. per 100 c.c. Kline test, negative. Spinal fluid, negative.

Radiological studies: Chest film revealed slight broadening of the aorta, otherwise the heart and lungs were within normal limits. A gastrointestinal roentgenographic series was negative. A roentgenogram of the sella turcica was negative. Gall-bladder visualization (Graham-Cole) revealed impaired contractility of the gall-bladder. An electrocardiogram showed myocardial damage, non-specific in type.

Repeated determinations of the basal metabolic rate gave the following results: July 23, +17; July 27, +18; July 30, +13; August 11, +41; August 16, +33; August 21, +35; September 10, +22; September 16, +28; September 20, +18; October 5, +26; and October 12, +1.

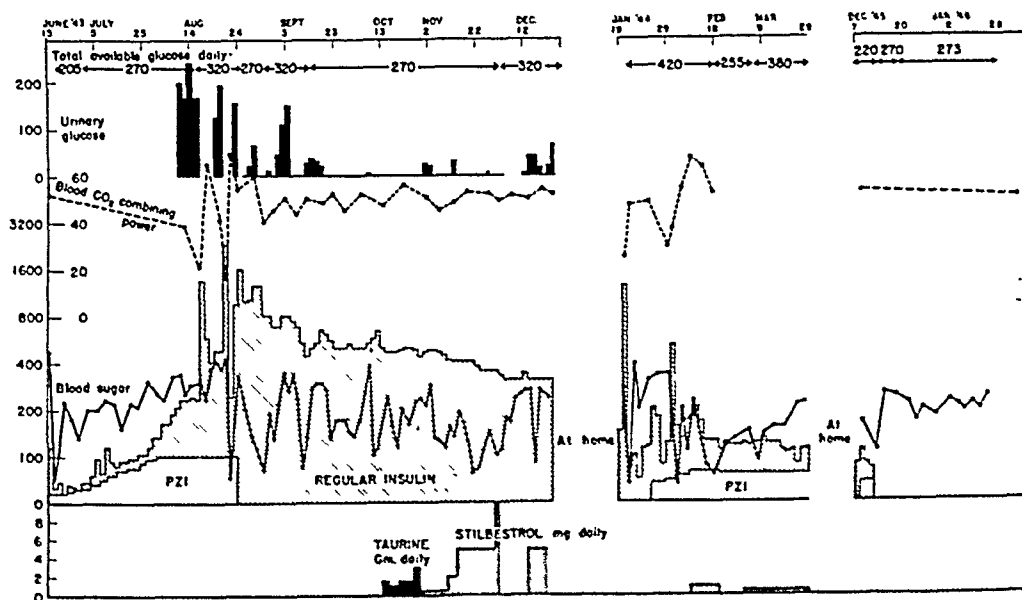


CHART 1.

The hospital course is represented graphically in chart 1. Upon admission on June 15 the blood sugar was 500 mg. per 100 c.c., and there was a 4+ glycosuria and a slight acetonuria. At seven o'clock the next morning, after a total of 20 units of protamine zinc insulin and 180 units of regular insulin given over a period of 18 hours, the blood sugar was 50 mg. per 100 c.c., the blood carbon dioxide combining power was 52 volumes per cent, and the urine was free of glucose and acetone. During the first two weeks in the hospital while on a diet of carbohydrates 150 grams, protein 80 grams, fat 90 grams with 20 to 30 units of protamine zinc insulin and 0 to 25 units of regular insulin daily, the fasting blood sugar was maintained between 100 and 230 mg. per 100 c.c. and fractional urinary specimens were negative for acetone and showed a 0 to 2+ glycosuria. The weight increased from 114 to 120 pounds during this period and the patient appeared normally sensitive to insulin.

TABLE II  
Insulin Sensitivity Tests

	Date	Type of Insulin	Route	Dose Units	Blood Sugars—mg. per cent Time										
					Fasting	15'	30'	45'	60'	75'	105'	120'	180'	240'	300'
Case I (N.E.)	8-14-43	Regular	I.V.	40	266	288		380		388	354				
	8-16-43	Regular	I.V.	100	308	332		346		354					
	8-19-43	Crystalline	I.V.	150	400	398		348		344					
	10-11-43	Regular	I.V.	100	95	95	91	80	59						
	3-9-44	Regular	I.V.	50	182	160	154	135	126						
	3-21-44	Regular	I.V.	50	172	150	146	140							
Case II (E.C.M.)	12-11-45	Regular	I.V.	25	109	127	102	103	84				47		56
	12-21-45	Regular	I.V.	25	218		200	200	180			123	94		
	1-11-46	Placebo (Saline)	I.V.		192	169	165	154	174			157	144	140	
	5-24-44	Regular	I.V.	25	332	330	338	304	308	294					
Case III (C.T.)	12-11-44	Regular	I.V.	25	240	236	240	216	220			214			
	12-21-44	Crystalline	I.V.	50	220	232	247	238	269						
	8-22-45	Regular	I.V.	25	206	204	200	202	202			194			
	8-31-45	Regular	I.V.	50	206	196	202	196	188			180			
	9-6-45	Regular and 5 c.c. liver	I.V.	50	208	187	183	185	169			172	148		
	12-11-45	Regular	I.V.	25	216	182	183	182				183	169		
	1-7-46	Regular	I.V.	50	140	138	146	145	130			131	131		

From June 29 until August 16 the fasting blood sugar was consistently elevated and fractional urinary specimens showed a 2+ to 4+ glycosuria, despite a progressive increase in insulin dosage to 100 units protamine zinc insulin and 140 units of regular insulin daily. Between August 9 and 15, while receiving insulin in the above doses along with a diet furnishing 270 grams available glucose daily, the patient excreted from 165 to 240 grams of glucose in the 24 hour urine specimen.

There were no local or general reactions to either form of insulin at any time. Intradermal tests with crystalline, regular and protamine zinc insulin gave no reaction. The passive transfer test was negative. There was no evidence of failure of absorption of the administered insulin. As a further check, sensitivity tests to intravenously injected insulin were performed (table 2). A thorough search for acute or chronic infection was negative. By this time it had become apparent that insulin resistance had developed.

Laboratory evidence of acidosis was first noted on August 12 when acetone appeared in the urine and the blood carbon dioxide combining power was 39 volumes per cent. Acidosis steadily deepened during the next four days. On the morning of August 16 the patient was stuporous and the carbon dioxide combining power was 21 volumes per cent. During the next 19 hours she received 2,000 c.c. Hartmann's solution, 2,000 c.c. saline and 1,500 units of regular insulin and 100 units of protamine zinc insulin. On the morning of August 17 the blood carbon dioxide combining power was 65 volumes per cent and the blood sugar was 240 mg. per 100 c.c. Despite daily doses of 400 to 610 units of insulin during the next four days, the patient slipped into severe acidosis on the morning of August 21, manifested by deep stupor, peripheral vascular collapse and a blood carbon dioxide combining power of 16 volumes per cent. During the next 16 hours she received 800 c.c. plasma, 3,000 c.c. Hartmann's solution, 1,000 c.c. saline, 2,150 units of regular insulin and 100 units of protamine zinc insulin. On the morning of August 22, 1943 the blood carbon dioxide combining power was 69 volumes per cent and the blood sugar 55 mg. per 100 c.c. Throughout that day only 250 units of insulin were required to keep the urine free of sugar and acetone. It is noteworthy that in this case, as well as in others in the literature, the hyperglycemia and acidosis in insulin resistant patients can be corrected if enough insulin is administered.

In the 16 day period from August 24, 1943 to September 10, 1943 the daily dose of insulin ranged from 700 to 1600 units of regular insulin, averaging 920 units. On a diet containing from 270 to 320 grams of available glucose, the urinary output of glucose averaged 50 grams daily. Fractional urinalyses gave 0 to 4+ glycosuria but no acetonuria. The fasting blood sugars ranged from 70 to 350 mg. per 100 c.c. Attempts at reducing the insulin dosage resulted in an increased glycosuria whereas substantial increases in the insulin dosage resulted in hypoglycemic reactions associated with blood sugars as low as 36 mg. per 100 c.c. During this period there was a definite tendency to a gradual reduction in the insulin requirement.

From September 10, 1943 to October 31, 1943, the patient was fairly well stabilized on regular insulin exclusively, the daily dosage ranging between 440 and 670 units and averaging 525 units. It was found that the diabetes was better controlled when 75 per cent to 100 per cent of the total daily dose was given in a single injection before breakfast. When a second injection was needed the optimal time was before the noon meal. A bedtime feeding was required to prevent nocturnal reactions, illustrating the prolonged effect of regular insulin when given in massive doses.

From October 15 to October 31 taurine was given in daily doses of 1 to 3 grams as a therapeutic measure, to be discussed below, but had no appreciable effect upon the diabetic state. The fasting blood sugar ranged between 100 and 250 mg. per 100 c.c. and the urine was generally sugar free.

Stilbestrol was started on October 31 in daily doses of 0.5 mg., which were increased to 2 mg. on November 10 and to 5 mg. on November 14, continuing until December 2. During this period the fasting blood sugar was generally within the normal range and the urine was usually sugar free. Insulin requirements gradually fell from 500 units at the beginning of stilbestrol therapy to 340 units at the end of the course. Stilbestrol was discontinued on December 2 in an effort to determine whether the improvement was related to or independent of stilbestrol therapy. During the following 10 days the blood sugar rose steadily and became stabilized in a zone between 240 and 280 mg. per 100 c.c. This, however, may have been due in part or in toto to a drop in insulin dosage to 320 units and an increase in dietary available glucose of 50 grams daily, rather than to estrogen withdrawal. Reinstitution of stilbestrol on December 14 in 5 mg. doses daily did not modify the hyperglycemia during the next eight days.

On December 24, 1943 the patient was discharged on a diet of carbohydrates 250 grams, protein 100 grams and fat 110 grams with instructions to take 320 units regular

insulin every morning before breakfast. No other medication was given. While at home the patient took less than the recommended doses of insulin and the diabetes was poorly controlled.

On January 19, 1944 at 11:00 p.m. the patient was readmitted, complaining of nausea and vomiting and an oppressive feeling over the precordium. She was acidotic, dehydrated, cold and pulseless. The blood pressure was unobtainable. The urine gave a 4+ reaction for both sugar and acetone. After receiving 1,275 units regular insulin and 5,000 c.c. of parenteral fluids, including 21 grams sodium bicarbonate in an 18 hour period, the patient was alert, the blood pressure was above shock level, and the urine was free from sugar and acetone. The carbon dioxide combining power of 25 volumes per cent taken nine hours after admission had risen to 42 volumes per cent nine hours later. On the morning of January 21, 1944 the blood sugar was 39 mg. per 100 c.c. and carbon dioxide combining power 45 volumes per cent.

Serial electrocardiograms were interpreted as indicative of acute ischemia of the anterior wall of the left ventricle, on the basis of deeply inverted cove-shaped T-waves associated with a normal QRS pattern in leads  $V_1$  through  $V_4$  inclusive. These abnormalities had completely disappeared by February 16, 1944.

During the 11 day period from January 21, 1944 to January 31, 1944 the daily insulin dose averaged only about 120 units, ranging from 50 to 200 units, and the diet contained 420 grams of available glucose. On this regimen the diabetic control was poor, the fasting blood sugars averaging over 300 mg. per 100 c.c. and the fractional qualitative urinalyses showing a 1+ to 4+ glycosuria with frequent traces of acetone. Protamine zinc insulin was started on January 26, 1944 and was given in daily doses of 40 to 65 units along with regular insulin for the remainder of the hospital stay.

On January 30, 1944 the patient had symptoms of a mild upper respiratory infection. The blood sugar was 369 mg. per 100 c.c. and the  $\text{CO}_2$  combining power, 29 volumes per cent. She received 2,500 c.c. of intravenous fluids, including 10 grams sodium bicarbonate, on that day in addition to 175 units of insulin. On the following morning the patient was in deep stupor and the urine gave a 4+ reaction for glucose and acetone. The temperature was  $103^\circ \text{F}$ . and there was evidence of an early bronchopneumonia. She was put on sulfathiazole therapy and in the next 24 hours was given 1,005 units of insulin and 4,500 c.c. of fluids intravenously, including 10 grams sodium bicarbonate. Again there was a prompt response, the blood sugar and  $\text{CO}_2$  combining power on the morning of February 1, 1944 being 28 mg. per cent and 54 volumes per cent respectively. The temperature was down to normal and remained so.

In the period from February 1, 1944 until discharge on March 29, 1944, the diabetes was fairly well controlled on a daily dose of insulin ranging from 205 to 80 units and averaging about 150 units. The dietary available glucose varied from 420 to 255 grams. On this regimen, the fasting blood sugars were usually well below 200 mg. per 100 c.c. and qualitative fractional urinalyses were consistently negative for acetone and showed a glycosuria of from 1+ to 2+.

Stilbestrol in daily doses of 0.5 to 1.0 mg. was given in the intervals between February 7, 1944 and February 21, 1944 and from February 29, 1944 until discharge. The insulin requirement had decreased greatly before this course of stilbestrol was instituted, the diabetes being fairly well controlled with a total of 160 to 180 units of insulin and a dietary available glucose of 420 grams. Shortly before discharge the diabetes was equally well controlled with 110 to 125 units of insulin daily and a dietary available glucose of 320 grams. This slight change was probably independent of estrogenic therapy. However, the stilbestrol dosage was sufficient to cause a marked reduction in urinary gonadotropic excretion. An assay carried out by Dr. Carl Heller<sup>22</sup> on October 4, 1943 before the first course of stilbestrol was started gave ovarian weight of 49.2 mg. in the assay rat. The urinary gonadotropic titer was

thus in the menopausal zone but was not excessively high. Upon repetition of the assay on March 20, 1944, while the patient was receiving 0.5 mg. of stilbestrol daily, no evidence of stimulation of either the uterus or ovaries of the assay rat was obtained. This was interpreted to indicate that the gonadotropins were absent from the 12 hour overnight urine specimen or else present in quantities too small to be detected by this method of assay.

On March 24, 1944 a hippuric acid test revealed a urinary excretion of 2.65 grams of benzoic acid which showed considerable improvement over the output of 1.87 grams in August, 1943, at the time of development of the insulin resistance. The improvement was also reflected in the serum proteins. A determination on March 24, 1944 gave values of 4.4 grams per 100 c.c. serum albumin and 2.4 grams serum globulin as compared with 2.9 grams per 100 c.c. serum albumin and 2.0 grams serum globulin in August, 1943. At no time was there any clinical evidence of hepatic disease.

Insulin sensitivity tests (table 2) performed on March 9, 1944 and March 21, 1944 showed a distinct improvement as compared to those carried out during the first admission. The results of these tests together with the marked reduction in her insulin requirement indicated a change in status from insulin resistance to insulin insensitivity.

From her discharge on March 29, 1944 until her last admission on December 7, 1945, the patient was followed at frequent intervals in the Out-Patient Department. Throughout this period she took a measured diet containing approximately 300 grams carbohydrate, 100 grams protein and 150 grams fat. Weight increased gradually during 1944 and maintained a plateau during 1945. Insulin dosage did not fall below 70 units daily and averaged 100 units daily throughout the period, 60 units of which were given as protamine zinc insulin, 40 units as regular insulin. Fairly good diabetic control was maintained throughout the entire 20 months.

On December 7, 1945, the patient was readmitted to the hospital because of a head injury sustained in an automobile accident. She was conscious but suffered from a headache and vomited repeatedly during the first 12 hours. Physical examination revealed a scalp laceration, an ulcerative gingivitis, but was otherwise essentially the same as in her previous entry. The blood pressure was 155 mm. Hg systolic and 90 diastolic and pulse 74. Roentgenogram of the skull showed no evidence of fracture. Chest ray and electrocardiogram showed no significant change.

Laboratory data: hemoglobin 11.0 gm.; white blood cells 12,550, with normal differential. Blood urea was 21 mg. per 100 c.c. Prothrombin 60 per cent. Bromsulphthalein test using 5 mg. per kilo and intravenous hippuric acid test were normal. Icterus index 16.6, falling subsequently to 8.9. Serum albumin was 4.5 gm., globulin 3.1 gm. per 100 c.c. Basal metabolic rate ranged from +14 to +24.

The patient remained afebrile and symptom free after the first 24 hours. She was given liquids until vomiting ceased, then was placed on a diet containing carbohydrate 175 grams, protein 70 grams, fat 50 grams, which was subsequently increased to carbohydrate 200 grams, protein 100 grams, and fat 150 grams. During the first four days in the hospital the patient received 40 units of protamine zinc insulin each morning plus 30 to 40 units of regular insulin daily. The admission urine gave a 2+ reaction for glucose and was negative for acetone. The following morning, after repeated vomiting, the urine was positive for acetone and gave a 3+ reaction for glucose, whereas the blood sugar was only 153 mg. per 100 c.c. Fractional urines thereafter were negative for acetone and showed a 0 to 3+ glycosuria.

From December 11, 1945, to January 28, 1946, the patient received no insulin except on those days when the insulin sensitivity tests were run. Throughout this period the fasting blood sugars varied between 170 mg. per 100 c.c. and 260 mg. per 100 c.c., and the fractional urinary specimens were negative for acetone and showed a 0 to 4+ glycosuria. There was no evidence of acidosis at any time during this



period. She was discharged to the Out-Patient Clinic on January 28, 1946, with instructions to follow the high caloric diet and to take no insulin.

Throughout the last six months, the patient was followed at frequent intervals in the Out-Patient Department. She followed the same diet and took no insulin. Fasting blood sugars ranged between 172 mg. per 100 c.c. and 272 mg. per 100 c.c., and the fasting urine specimens showed a 1 to 4+ glycosuria with positive acetone on only one occasion. The patient has maintained her weight at 112 to 115 pounds and when last seen was without complaint.

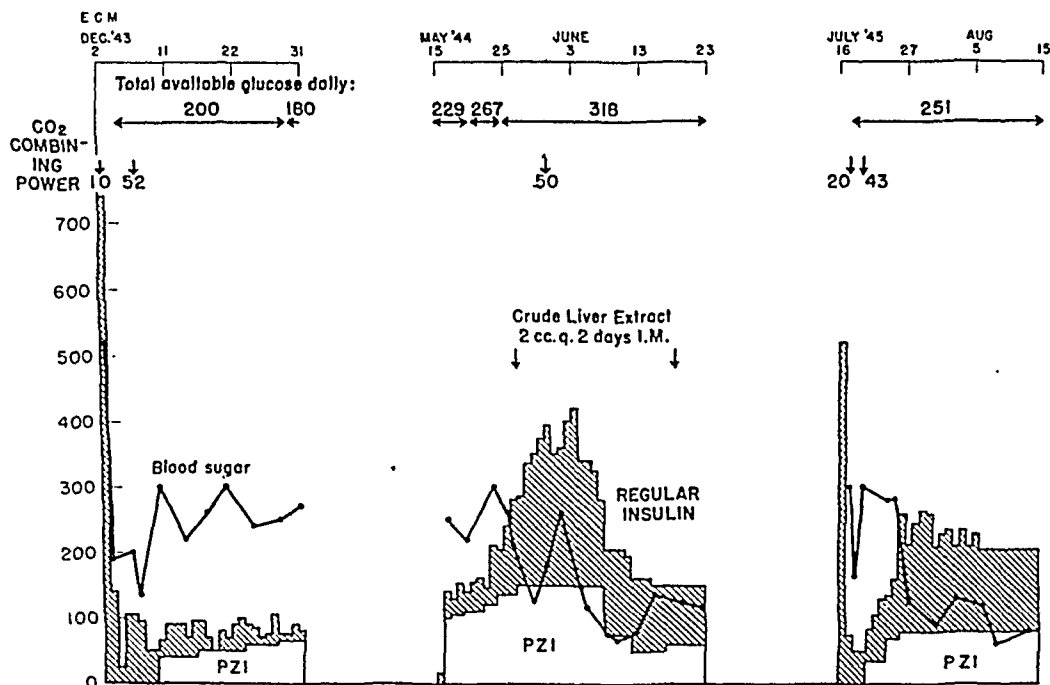


CHART 2.

*Case 2 (Chart 2).* E. C. M., a colored female, age 42, was first admitted on December 2, 1943. Diabetes mellitus had developed two years previously and had been treated at another clinic with protamine zinc insulin in doses of 120 units daily supplemented by small amounts of regular insulin. In November, 1943, the patient, on her own responsibility, gradually reduced the insulin dosage. By the end of the month she vomited repeatedly, then became drowsy and went into coma 12 hours before admission. Past history negative except for hysterectomy in 1937. There was no personal nor family history of allergy.

Physical examination revealed a well developed and nourished but markedly dehydrated female in deep coma. There was marked hyperpnea and the breath gave a strong odor of acetone. Optic fundi were negative. There was marked dental caries and pyorrhea. There were no signs of hyperfunction of the pituitary, adrenal or thyroid. The lungs and heart were negative. Blood pressure 110 mm. Hg systolic and 68 diastolic. Abdomen, back and extremities were negative. Hemoglobin 11.5 gm., white blood cells 10,200, filamentous 52 per cent, non-filamentous 22 per cent, lymphocytes 23 per cent, monocytes 2 per cent, eosinophiles 1 per cent. Blood urea was 48 mg. per 100 c.c. Blood cholesterol 139 mg. per 100 c.c.

Course during first admission: On entry the blood sugar was 520 mg. per 100 c.c., and the blood CO<sub>2</sub> combining power was 10 volumes per cent. The patient became mentally clear within 12 hours and acetone and diacetic acid disappeared from

the urine 20 hours after admission. During this period she received 740 units of regular insulin and 6,000 c.c. parenteral fluids. After recovery from the coma it became apparent that the patient had an upper respiratory infection which was accompanied by an average temperature of 100° F. A roentgenogram of the chest soon after admission showed congestion in both lung fields chiefly at the inner bases. All symptoms cleared within one week without complication.

Following recovery from acidosis, the patient was placed on a diet consisting of carbohydrate 150 grams, protein 70 grams, fat 100 grams and received 65 units of protamine zinc insulin daily, supplemented by 10 to 30 units of regular insulin. The fasting blood sugars ranged between 200 and 320 mg. per 100 c.c. and fractional urines revealed a 1+ to 3+ glycosuria, but were negative for acetone. Four carious teeth were extracted without complication.

On December 31, 1943 she was discharged with instructions to take a diet consisting of carbohydrate 150 grams, protein 70 grams, fat 80 grams, and protamine zinc insulin 70 units every morning plus 15 units of regular insulin before her noon meal.

On March 14, 1944 diet was increased to provide carbohydrate 200 grams, protein 100 grams, fat 120 grams which permitted slow gain in weight. As a result of gradual increase in insulin dosage to 100 units of protamine zinc insulin and 45 units of regular insulin daily, diabetes was controlled fairly well until May, 1944 when polyuria and polydipsia supervened, leading to hospitalization.

The admission blood sugar was 256 mg. per 100 c.c. and the urine gave a 4+ reaction for sugar with a trace of acetone. The patient was well hydrated, mentally clear, and in no apparent distress. Physical examination was essentially negative except for a slight decrease in vision and a slight pyorrhea.

Laboratory data: hemoglobin 12.0 grams, white blood cells 6,450. Normal differential. Blood urea, cholesterol, calcium, phosphorus were normal. Blood chlorides 518 mg. per 100 c.c. Blood CO<sub>2</sub> combining power 50 volumes per cent. Hippuric acid test showed excretion of 1.64 grams of benzoic acid on May 22, and 2.8 grams on June 5. Bromsulphthalein test was normal on two occasions. Serum albumin 3.6 gm. per 100 c.c., globulin 3.9 gm. per 100 c.c. Repeated urinalysis revealed normal sediment. Kline test negative. Basal metabolic rate +1 on June 6. Chest roentgenogram revealed clearing of the previous bilateral congestion.

Clinical course of second admission: The initial diet supplied 229 grams of available glucose daily and was increased on the sixth day to provide 267 grams and on the tenth day to 318 grams. This diet was continued for the remaining four weeks of hospitalization and was distributed as follows: carbohydrate 250 grams, protein 100 grams, fat 100 grams. The initial insulin dosage of 100 units protamine zinc insulin supplemented by 30 to 50 units of regular insulin daily was inadequate and was progressively increased during the first two weeks to 150 units of protamine zinc insulin and 250 units of regular insulin daily. There was a constant glycosuria and hyperglycemia until total daily insulin dosage reached 400 units, at which time the diabetes was brought under control. The urine was consistently negative for acetone throughout this period and there was no evidence of infection. The increased insulin requirement was disproportionate to the more liberal carbohydrate intake and was attributed to increased insulin resistance. Further evidence in support of this hypothesis was obtained on May 24 when the patient exhibited no response to 25 units of regular insulin given intravenously (see table 2).

After the diabetes was brought under control the insulin requirement progressively decreased. Satisfactory control was maintained during the week prior to discharge by 50 units of protamine zinc insulin and 90 units of regular insulin daily. Crude liver extract was started at the height of insulin resistance and was given in 2 c.c. doses intramuscularly every other day for the remainder of the hospital stay. The

reduction of insulin requirements from 400 to 140 units daily which occurred during the period of liver extract administration could be explained by improved diabetic control together with spontaneous reduction of insulin resistance and thus could not be ascribed definitely to the liver therapy on the basis of the evidence at hand.

During the 13 months which elapsed since discharge from the hospital on June 23, 1944 and the patient's last admission, she was again followed at frequent intervals in the Out-Patient Department. She continued to gain weight on a diet of carbohydrate 250 grams, protein 100 grams, fat 100 grams and was maintained in fair diabetic control. The daily insulin varied from protamine zinc insulin 100 units supplemented with regular insulin 60, 60, 15, to protamine zinc insulin 75 and regular insulin 105 in mixture given in one daily morning injection.

On November 30, 1944 stilbestrol was started in doses of 1 mg. daily. On December 8, 1944 the dosage was increased to 2 mg. daily and on December 28, 1944 to 3 mg. daily. Stilbestrol was stopped on January 11, 1945, when the patient complained of swollen face and wrists. However, it was started again as 2 mg. daily January 25, 1945, and continued through February, 1945, without ill effect and without marked effect on the diabetic control.

On July 16, 1945, the patient was again admitted to the hospital in diabetic acidosis precipitated by bilateral thigh abscesses. Physical examination on admission revealed drowsiness, slight hyperpnea and moderate dehydration. Blood pressure 130 mm. Hg systolic and 90 diastolic. The remainder of the physical examination was essentially negative except for fluctuant abscesses on the anterolateral aspects of both thighs. The urine on admission gave a four plus reaction for both sugar and acetone. Blood sugar taken approximately 12 hours after admission was 298 mg. per 100 c.c. and  $\text{CO}_2$  combining power was 20 volumes per cent. After receiving 465 units of insulin and 2,000 c.c. of parenteral fluids in a 24 hour period, the patient was alert and the urine was acetone free.

The patient's temperature ranged between 100° and 102° F. until the third day when the abscesses were incised and drained. Culture of the purulent material revealed *B. Coli* and *Staphylococcus albus*. The temperature was normal for the remainder of hospitalization. The patient was served a diet supplying 251 grams available glucose daily, distributed as follows: carbohydrate 190 grams, protein 90 grams, fat 90 grams.

Regular insulin was given at frequent intervals in accordance with urinalyses until defervescence, when protamine zinc insulin was started in dose of 35 units supplemented by 50 units of regular insulin daily. This dosage was grossly inadequate and had to be increased during the course of the next week to protamine zinc insulin 80 units and regular insulin 190 units daily in order to bring the diabetes under control.

Prior to discharge the diabetes was well controlled by daily doses of 80 units of protamine zinc insulin plus 130 units of regular insulin. Since all traces of infection and acidosis had disappeared it was evident that the patient was still insulin resistant.

The patient was discharged to the Out-Patient Department August 15, 1945, on the diet of carbohydrate 190 grams, protein 90 grams, fat 90 grams, and protamine insulin 80 units, regular insulin 130 units taken in the morning in one injection as a mixture. Soon after discharge the insensitivity to insulin gradually diminished, permitting progressive reduction in her daily insulin dosage until the total dosage dropped to 140 units (protamine 35 units, regular 105 units). The patient was without complaint, working every day and maintaining her weight.

*Case 3 (Chart 3).* C. T., a 54 year old colored male, was admitted to the hospital on October 23, 1944 because of uncontrolled diabetes and a carbuncle of the neck. Diabetes mellitus had been discovered in 1941 and was controlled on an average dose of 35 units protamine zinc insulin daily up until March, 1943, when the patient dis-

continued insulin against the advice of his physician. Shortly afterwards, polyphagia, polydipsia and polyuria set in. In November, 1943 he began to have numbness and burning of the feet. He continued at work until June, 1944, when he was forced to quit because of weakness and nervousness. Since then he had had an indolent ulcer of the right great toe. During this period he lost weight steadily in spite of a good appetite. Three days before admission a carbuncle developed on the back of the neck. During the 12 hours immediately preceding entry he vomited several times and became stuporous and delirious.

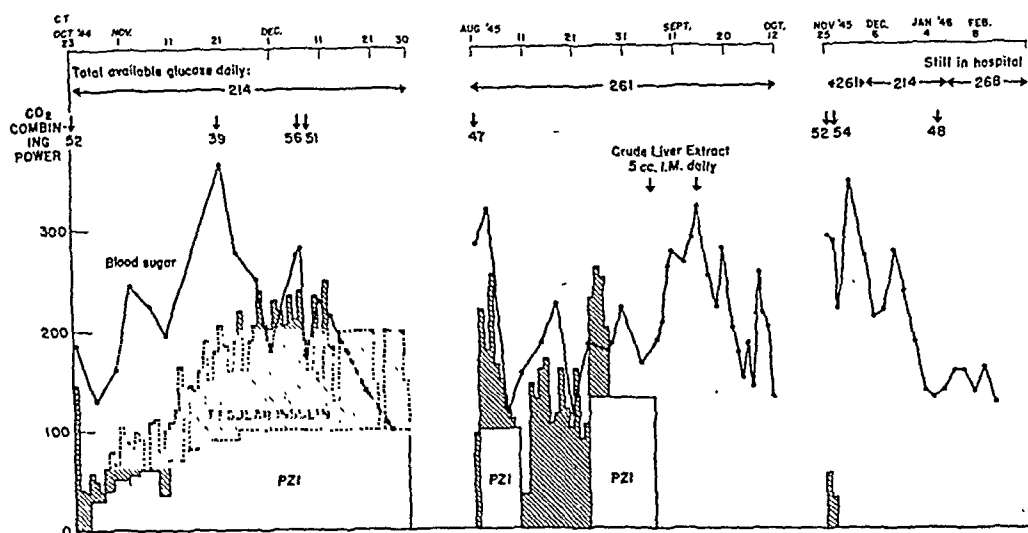


CHART 3.

Past history, including history by systems, was irrelevant. There was no personal nor family history of allergy.

Physical examination revealed a stuporous colored male, who showed no clinical signs of diabetic acidosis. The pupils were equal and regular and reacted to light and accommodation. The retinal arteries exhibited Grade 2 narrowing and sclerosis, and there were a few superficial linear hemorrhages, which were thought to be hypertensive rather than diabetic in etiology. There was no edema of the optic disk or retina. There was marked dental caries and pyorrhea. Cranial nerves were normal except for partial eighth nerve deafness on the left. The thyroid was not palpable and there were no clinical signs of hyperfunction of the pituitary, adrenal or thyroid. There was an indurated carbuncle on the back of the neck 5 by 8 cm. in diameter. The heart was moderately enlarged to the left and there was a soft blowing systolic murmur at the apex, attributed to relative mitral insufficiency. The aortic second sound was accentuated. Blood pressure 200 mm. Hg systolic and 100 diastolic. Lungs were clear. A firm liver edge was palpable one finger's-breadth below the costal margin. There was no evidence of portal obstruction. There was a small, well healed penile scar. A non-infected trophic ulcer was present on the plantar surface of the right great toe. Patellar and Achilles reflexes were absent. There was moderate tenderness over both sciatic nerves. There was hypalgesia of both feet and legs, exhibiting a jagged upper border typical of a peripheral lesion. Sense of motion and position was intact in the feet. Vibratory sense was definitely diminished over both malleoli and tibiae. There was moderate weakness of the dorsiflexors of both feet. The dorsalis pedis and left posterior tibial pulses were not obtained. The femoral and popliteal pulses were of good quality.

Laboratory data: hemoglobin 12 gm., white blood cells 10,100, 67 per cent neutrophils, 26 per cent lymphocytes, 7 per cent monocytes. Subsequently the white blood count fell to normal. The admission urine specimen gave a four plus test for sugar, but was negative for acetone. Blood urea was 48 mg. per 100 c.c., serum albumin 3 gm. per 100 c.c., globulin 3.5 gm. Bromsulphthalein test on two occasions was entirely normal. In the oral hippuric acid test, 3.26 gm. benzoic acid were excreted. Blood Kline and Kahn tests were positive. Spinal fluid was clear and dynamics were normal. Cell count, 2 per cu. mm., 88 per cent of which were lymphocytes. The Kline test in the spinal fluid was doubtful. Colloidal gold, 2222331100. Basal metabolic rate was plus 21 on November 28, plus 40 on November 30, and plus 27 on December 5. Chest roentgenogram revealed no evidence of tuberculosis.

The clinical diagnosis was diabetes mellitus, essential vascular hypertension, peripheral arteriosclerosis, peripheral neuritis, central nervous system syphilis, possible masked hyperthyroidism.

The temperature was 102° F. on admission and rapidly fell to normal following drainage of the carbuncle. The temperature was consistently normal after October 26 and the carbuncle and the ulcer of the toe gradually healed.

Upon admission on October 24 the blood sugar was 185 mg. per 100 c.c. and the blood carbon dioxide combining power was 52 vol. per cent. The diabetes was brought under control rapidly with regular insulin and by the end of the first week it seemed well stabilized by 30 units of protamine zinc insulin supplemented by 16 units of regular insulin daily. Antiluetic therapy was instituted and continued throughout hospitalization. At this time the patient was taking a diet consisting of carbohydrate 160 grams, protein 80 grams, fat 80 grams. This diet was maintained throughout the period of hospitalization.

From November 1 until December 17, the fractional urines gave a consistent two plus to four plus reaction for glucose but were negative for acetone. Fasting blood sugars during this period ranged between 174 and 363 mg. per 100 c.c. The protamine zinc insulin was gradually increased to a maximum of 100 units on November 27 and maintained at that level until discharge. Supplements of regular insulin were given according to urinary reaction and had to be gradually increased to a range of 100 to 150 units daily when the diabetes was finally brought under control. At no time was there evidence of either local or general allergic reactions to insulin. The insulin requirements which for a time reached 250 units daily were finally stabilized at 200 units daily before discharge. There was no evidence of infection or acidosis during this period and the cause of the developing insulin resistance was not discovered.

On December 30, 1944, the patient was discharged on the same diet plus protamine zinc insulin 100 units and regular insulin 100 units, and was seen at frequent intervals in the Out-Patient Department. Throughout the first six month period, the patient persistently gained weight. His blood sugars ranged from 163 to 366 mg. per 100 c.c. with a tendency to sugars over 300 throughout the last month.

On August 1, 1945, the patient was readmitted with a history of stopping all insulin two to three weeks previously. Complaints at this time consisted of a pain behind his right ear one day in duration, staggering gait and slurring speech. Physical examination revealed a confused stuporous colored male without clinical signs of acidosis. The pupils were equal and reacted to light. Fundi revealed a Grade 2 hypertensive change in the arterioles with numerous yellowish, opaque exudate and superficial flame-shaped hemorrhages—the left fundus revealed a large fresh papillary hemorrhage. There was a left facial paresis and weakness in the left hand. Blood pressure 180 mm. Hg systolic and 115 diastolic. Other physical findings essentially as on first entry. On admission the blood sugar was 284 mg. per 100 c.c. and carbon dioxide combining power was 47 volumes per cent. Clinical impression: diabetes mellitus uncontrolled; general paresis.

Laboratory data: hemoglobin 10.0 grams, white blood cells 5,150 with normal differential. Repeated studies of urinary sediment were essentially normal. Blood urea 37 mg. per 100 c.c. Plasma cholesterol ranged from 414 mg. per 100 c.c. to 370 mg. per 100 c.c. Prothrombin was 82 per cent of normal. The serum albumin was 2.9 grams per 100 c.c.; globulin 4.3 grams per 100 c.c. With the intravenous hippuric acid test, 1.4 grams benzoic acid were excreted. The spinal fluid was clear and under normal pressure. Cell count 4 per cubic millimeter. Spinal fluid Kline positive. Colloidal gold, 1112211100. The chest roentgenogram revealed left ventricular enlargement. The sella turcica appeared normal on roentgen-ray.

The patient was maintained on a diet consisting of carbohydrate 200 grams, protein 90 grams, fat 90 grams throughout hospitalization. Except for the first three days after admission, the patient's course was afebrile. Only minimal residual paresis of the left hand was present at discharge.

From August 2, 1945, to August 9, 1945, patient received 100 units of protamine zinc insulin daily supplemented with regular insulin to urine reaction. Total daily regular insulin varied from 0 to 155 units. Fractional urines showed a negative to three plus glycosuria and negative acetone. Two fasting blood sugars during this period were 320 mg. per 100 c.c. and 117 mg. per 100 c.c. respectively.

From August 10 to August 23, the patient was placed on regular insulin in accordance with urinary reaction. Fractional urines varied from negative to four plus with the majority of specimens showing a three plus glycosuria, without acetone. The total daily insulin again varied widely, ranging from 45 to 170 units. Fasting blood sugars ranged from 114 mg. per 100 c.c. to 224 mg. per 100 c.c.

In the period from August 24 through August 27, the patient was returned to protamine zinc insulin with supplementary regular insulin. This was continued for four days and then on August 28 through September 5, 130 units of protamine zinc insulin were given daily without regular insulin. The fractional urinary specimens continued to show a negative to four plus glycosuria, no acetone. During this period, fasting blood sugars ranged between 178 mg. per 100 c.c. and 218 mg. per 100 c.c.

On September 6 until discharge, October 12, all insulin was discontinued. Between September 6 and September 15 the patient received 5 c.c. of liver extract daily intramuscularly. The fractional urinary specimens during this 10 day period showed but slight change over those of previous periods when various combinations of insulin were used. The urinary specimens varied from 0 to four plus glycosuria, but contained no acetone. Daily fasting blood sugars ranged between 189 mg. per 100 c.c. to 322 mg. per 100 c.c. with noticeable trend of rising blood sugar level toward the end of the period of liver therapy.

From September 16 until October 12, the patient received no medication. The diet was maintained at carbohydrate 200 grams, protein 90 grams, fat 90 grams. The fasting blood sugars ranged between 132 mg. per 100 c.c. (October 5) to 280 mg. per 100 c.c. Fractional urinary specimens varied from negative to four plus glycosuria and were consistently negative for acetone. The patient was discharged to the Out-Patient Department on the foregoing diet with instructions to take no insulin.

On November 25, 1945, the patient was readmitted to the hospital because of disorientation and irrationality of 24 hours' duration. Examination revealed a well developed, well nourished negro male with no clinical signs of acidosis. On first examination patient was confused, dysarthric, irrational, disoriented and generally uncoöperative. The other findings were essentially as described above. Blood pressure 190 mm. Hg systolic and 120 diastolic. On admission the blood sugar was 292 mg. per 100 c.c. and the carbon dioxide combining power was 52 volumes per cent.

Laboratory data: hemoglobin 11 grams, white blood cells 8,000 with normal differential. The admission urine specimen gave a four plus glycosuria, no acetone. The blood urea was 21 mg. per 100 c.c. Serum proteins (December 10, 1945), albumin

2.6 gm. per 100 c.c., globulin 3.9 gm.; on December 28, 1945, albumin 2.8 gm. per 100 c.c., globulin 4.0 gm. The plasma cholesterol was 231 mg. per 100 c.c. The bromsulphthalein test was normal. By intravenous hippuric acid test 0.46 gram benzoic acid was excreted. Icterus index was 10.7 on December 5, 1945, and 10 on December 28, 1945. Prothrombin 70 per cent of normal on December 4 and 100 per cent on December 28. Blood Kahn and Kline tests positive. Spinal fluid clear, normal dynamics, no cells, only trace of globulin. Spinal fluid Kline test positive. Colloidal gold 2223321100. Basal metabolic rate on December 21, 1945, was plus 7 per cent.

A low grade fever reaching a maximum of 102° (R) was present from admission to December 8, 1945, after which the temperature was normal. This fever was attributed to bronchopneumonia. The initial chest roentgen-ray revealed a small area of bronchopneumonia which gradually resolved.

From November 26 to November 30, the patient was placed on a diabetic diet consisting of carbohydrate 200 grams, protein 90 grams, fat 90 grams, and received 55 units of regular insulin the first day and 30 units the second day and none thereafter.

During the febrile period fasting blood sugars ranged between 200 and 344 mg. per 100 c.c., but urines were consistently free of acetone. After defervescence the fasting blood sugar gradually fell and finally ranged between 101 mg. and 292 mg. per 100 c.c. At this time the patient was taking a diet furnishing 268 grams available glucose and received no insulin, except on days of intravenous sensitivity tests. Even at this time a significant drop in blood sugar did not occur following an intravenous injection of 50 units of regular insulin. The mental confusion cleared within a week and throughout the remainder of the hospitalization the patient was very coöperative although his reactions were slow. A final diagnosis of paresis was made and the patient was committed to a psychiatric institution.

## EXPERIMENTAL STUDIES

An experimental study was conducted to determine whether or not the alleged "insulin antagonist"<sup>20, 21, 22, 23, 27, 28, 29, 30, 31, 32</sup> could be detected in the sera of the three patients studied. The problem was approached in two ways, (1) an in vitro procedure in which insulin was incubated with the patient's serum for varying periods and then injected into rabbits under standardized conditions to determine its potency; and (2) an in vivo procedure in which the effect of the injection of the patient's serum on the insulin sensitivity of rabbits was determined.

## PROCEDURE

The following procedure was used for the in vitro study. A blood sample (25 to 50 c.c.) was withdrawn under aseptic conditions from the patient after 12 hours fasting and usually 12 hours after the last administration of insulin. The blood was allowed to clot, was centrifuged, and the serum was mixed with insulin of known potency. The mixture was incubated at 37.5° for varying intervals and then its potency was determined in rabbits weighing 2 plus or minus 0.5 kilos and fasted 24 hours. The Folin-Wu blood sugar method was employed. The mixture was administered intravenously in an amount containing either 5.0 units or 1.5 units

of insulin per kilo body weight. Comparable control rabbits received insulin incubated with the sera of normal subjects at the same dosage levels.

The *in vivo* procedure was conducted as follows: 20 c.c. of the patient's serum were injected intravenously into rabbits whose insulin response had been previously determined. After seven days, the response of the animal to a standard dose of insulin (1.5 units per kilo) was determined.

## RESULTS

The results obtained using the "*in vitro*" procedure are summarized in table 3.

It is evident that no indication of the presence of an "insulin antagonist" was found in any of the sera after periods of incubation with insulin, varying from 0 to 72 hours. In every case, the depression of blood sugar values in the rabbits injected with the incubated insulin-serum mixture was almost

TABLE III  
Effect of Incubating Insulin with Patient's Sera for Varying Intervals

Time After Injection of Incubated Insulin	Blood Sugar—(mg. per cent)—Incubation Time														
	0 Hours		4 Hours		24 Hours			48 Hours		72 Hours					
	Control*	Case I*	Control*	Case I*	Control*	Cases		Control*	Case I*	Control*	Case I*	Control**	Case I**	Case II**	Case III**
						I*	II*								
Fasting	90	94	93	113	109	95	154	—	105	89	95	114	103	95	94
20 min.	58	64	52	87	60	54	41	—	76	53	62	60	60	70	48
40 min.	53	45	28	41	59	54	38	—	50	53	37	59	62	55	46
60 min.	45	45	24	35	60	45	36	—	43	49	40	64	57	63	53
90 min.	43	40	35	29	66	41	37	—	38	49	40	56	52	60	65
120 min.	39	33	23	30	58	30	37	—	43	60	43	56	45	61	82

\* Dose = 5 units per kilo body weight, given intravenously to a 2.0 plus or minus 0.5 kilo rabbit fasted 24 hours.

\*\* Dose = 1.5 units per kilo body weight.

TABLE IV  
Effect of Injecting Patient's Serum on Insulin Sensitivity of Rabbit

Time After Insulin Injection*	Blood Sugar—mg. per cent	
	Control	Serum Case I
Fasting	114	103
20 min.	60	50
40 min.	59	52
60 min.	64	52
90 min.	56	45
120 min.	56	40

\* Dose = 1.5 units per kilo body weight, given intravenously to a 2.0 plus or minus 0.5 kilo rabbit fasted 24 hours. Rabbits had been injected 20.0 c.c. of control (normal) or patient's serum 7 days previously.



identical with that observed in control rabbits given insulin incubated with normal sera.

The results obtained using the "in vivo" procedure are given in table 4.

Again there was no evidence of an "insulin antagonist" in the serum of Case 1. The response to insulin after serum administration was no different from before.

## DISCUSSION

1. Etiology of the Insulin Resistance: The known factors responsible for insulin resistance have been summarized in table 1.

In each of the three cases reported in this communication, an attempt was made to investigate each of these factors.

Failure of absorption was excluded in each case by the lack of response to intravenously injected insulin. The possibility of excessively rapid excretion was not directly investigated but was considered unlikely in view of the refractoriness to large doses of insulin given subcutaneously at frequent intervals.

No leukocytic abnormalities were found in our cases. Although no assays were made for diabetogenic hormone or adrenal steroids, the possibility of excessive output of these hormones was extremely remote in view of the lack of clinical manifestations. There was no clear cut clinical evidence of hypothalamic disease in any of our three cases but the possibility of a lesion in this region could not be excluded in Case 3 (C. T.) who was known to have central nervous system lues. In Case 1 (N. E.) and Case 3 (C. T.) the basal metabolic rate was at the upper limits of normal at the inception of the insulin resistance, and subsequently fell spontaneously to normal. Since neither patient exhibited clinical manifestations of hyperthyroidism during the period when the metabolic rate was elevated, it was felt that these readings did not represent true basal levels but merely reflected the altered metabolism consequent upon the poor diabetic control. It was also noteworthy that both of these cases had an elevated blood cholesterol instead of the depression which would have been expected if hyperthyroidism were present.

No clinical manifestation of allergy was exhibited by any of our cases. Insulin intradermal and passive transfer tests were negative in N. E. (Case 1). Incubation of the serum of each of the three patients with insulin and subsequent injection of the mixture into rabbits gave no evidence of insulin neutralizing antibodies. The fall of blood sugar of the test rabbits was almost identical with that obtained with the same animals given a similar dose of insulin which had been incubated with the serum of a normal patient. From these studies it was concluded that no insulin-neutralizing antibodies were demonstrable in the blood sera.

Each of our patients showed evidence of insulin resistance at periods when there was no acidosis and no demonstrable infection. Although none

of the patients revealed clinical signs of hepatic disease, liver function as judged by the hippuric acid tests and the level of the plasma proteins was impaired in N. E. (Case 1) and E. C. M. (Case 2) at the height of their resistance and reverted to normal after disappearance of the insulin resistance. The moderate impairment of hepatic function was probably the result of the poor diabetic control during the period of insulin resistance rather than a cause of the insulin resistance. C. T. (Case 3) exhibited gradual depression of hepatic function during the two and a half year period of observation. However, his insulin requirements were as high or higher during the first admission when his liver function tests were practically normal as in subsequent admissions when his liver function tests were impaired.

An abnormal capacity of the tissues of these patients to destroy insulin remains as a possibility which can neither be definitely established nor excluded. With this reservation these cases must be classified in the group of unknown etiology.

2. Therapy: Where the cause for insulin resistance is apparent, such as acidosis or infection, improvement may be expected upon removal of the cause. When the etiology, as in our cases, is unknown, no specific therapeutic measures are available. The necessity for giving sufficient amounts of insulin when resistance is complicated by infection or acidosis has already been emphasized. The glycosuria and acidosis under such circumstances can be controlled if adequate amounts of insulin are administered, but as much as 1,000 to 5,000 units per day may be necessary. In our cases, the diabetes was better controlled when the insulin was given in single large doses rather than in multiple smaller doses.

A diet relatively high in carbohydrates and protein was used in all three cases in an effort to increase sensitivity to insulin and to improve liver function. The amount of available glucose in the diet of each patient was varied from time to time but no direct relationship could be found between glucose intake and insulin resistance.

Taurine was administered in Case 1 (N. E.) because of the claim by Macallum et al.<sup>53</sup> that this substance, as well as certain other sulfone derivatives, has a marked potentiating effect on insulin in the rabbit. This observation was not confirmed in our patient.

Stilbestrol was given in Cases 1 and 2 because of claims that estrogens increase sensitivity and reduce the requirement of insulin.<sup>54, 55, 56</sup> Although the diabetes was somewhat better controlled (Case 1) after the institution of stilbestrol therapy on each of the two admissions, the periods on and off stilbestrol were not sufficiently long and the diabetic control not sufficiently well standardized to justify any definite conclusions regarding the effect of stilbestrol on the diabetes. The results were merely encouraging enough to justify a more adequate trial of estrogens in future cases.

The greatest reductions in insulin requirements in our cases seemed to occur spontaneously and apparently independent of therapy. For this reason, great caution must be exercised in evaluating therapeutic measures employed in patients resistant to insulin.

### SUMMARY

Three cases of diabetes mellitus have exhibited spontaneous development and subsequent recession of insulin resistance during a two to three year period of close observation.

The known causes of insulin resistance are summarized in tabular form and were investigated in each case. The investigations included studies for the presence of insulin neutralizing antibodies and were completely negative in all cases. The cause of insulin resistance in these cases remains unknown.

The necessity for giving sufficient amounts of insulin in the presence of complicating acidosis or infection has been emphasized. The maximum daily insulin requirement reached 2,150 units in one of these cases. The various therapeutic measures included taurine and stilbestrol, but it was concluded that the improvement in each case was spontaneous and unrelated to therapy.

### BIBLIOGRAPHY

1. MARTIN, W. P., MARTIN, H. E., LYSTER, R. W., and STROUSE, S.: Insulin resistance, critical survey of the literature with the report of a case, *Jr. Clin. Endocrinol.*, 1941, i, 387-397.
2. GOLDNER, M. G., and CLARK, D. E.: The insulin requirement of man after total pancreatectomy, *Jr. Clin. Endocrinol.*, 1944, iv, 194-197.
3. BRUNSCHWIG, A., RICKETTS, H. T., and BIGELOW, R. R.: Total pancreatectomy, total gastrectomy, total duodenectomy, splenectomy, left adrenalectomy and omentectomy in a diabetic patient, recovery, *Surg., Gynec. and Obst.*, 1945, lxxx, 252-256.
4. LOZINSKI, E., and FROHLICH, L. I.: Resistance to insulin, *Canad. Med. Assoc. Jr.*, 1942, xlv, 62-65.
5. TAUSSIG, A. E.: A case of diabetes mellitus refractory to insulin, *Trans. Assoc. Am. Phys.*, 1927, lxii, 166-177.
6. ROOT, H. F., et al.: Absorption of insulin labeled with radioactive iodine in human diabetes, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 84-90.
7. KARELITZ, S., LEADER, S. D., and COHEN, P.: Insulin inactivation by human blood cells and plasma in vitro, *Arch. Int. Med.*, 1930, xlv, 690-701.
8. MARBLE, A.: Insulin resistance, report of a case of marked insensitiveness of long duration without demonstrable cause, *Arch. Int. Med.*, 1938, lxii, 432-446.
9. LEVI, J. E., and FRIEDMAN, H. T.: Insulin resistance in a case of diabetes mellitus and chronic lymphatic leukemia, *New England Jr. Med.*, 1941, ccxxv, 975-978.
10. ROCCA, F., and POLLACK, E.: Action of estrone on extrapancreatic factors of insulin resistant diabetes, *Rev. méd. latino-am.*, 1942, xxviii, 23; abstracted, *Jr. Am. Med. Assoc.*, 1943, cxxii, 471-472.
11. YOUNG, F. G.: Growth and experimental insulin-insensitive diabetes, *Brit. Med. Jr.*, 1944, ii, 715-718.
12. PEYSER, E.: Antiinsulin effect of desoxycorticosterone acetate, *Verhandl. Ver. schweiz. Physiol.*, 1941, xxviii, 42-43; *Chem. Abstracts*, 1944, xxxviii, 5550 (abstracted).

13. PULLEN, R. L., and SODEMAN, W. A.: Diabetes mellitus associated with hirsutism and unusual insulin resistance, *Jr. Clin. Endocrinol.*, 1943, iii, 345-350.
14. HART, F. D., and GREENE, R.: Quiescent acromegaly with insulin-resistant diabetes, *Proc. Roy. Soc. Med.*, 1941, xxxv, 17-18.
15. WISLICKI, L.: The antagonism between the posterior pituitary lobe and insulin, *Jr. Physiol.*, 1943, cii, 274-280.
16. WARVEL, J. H.: Insulin resistance in a patient with possible pinealoma tumor and cyst of the pituitary (case report), *Jr. Nerv. and Ment. Dis.*, 1940, xci, 342-343.
17. ALTSCHULER, S. S., and GOULD, S. E.: Diabetes refractory to insulin, with report of a case, *Ann. Int. Med.*, 1936, ix, 1595-1602.
18. MASON, E. H.: The life history of a diabetic who acquired an unusual tolerance to insulin (case report), *Jr. Clin. Invest.*, 1930, ix, 31.
19. HILLS, R. G., SHARPE, J. C., and GAY, L. N.: Diabetes mellitus and hyperthyroidism, *Bull. Johns Hopkins Hosp.*, 1934, lv, 193-200.
20. ZECKWER, I. T.: Some atypical responses of rabbits to insulin, *Am. Jr. Physiol.*, 1933, cvi, 273-282.
21. SCHREIER, H.: Report of clinical and experimental findings in an insulin-refractory case of diabetes mellitus, *New York State Jr. Med.*, 1943, xliii, 1341-1343.
22. LOWELL, F. C.: Immunologic studies in insulin resistance, *Jr. Clin. Invest.*, 1944, xxiii, 225-231, 233-239.
23. KARR, W. G., SCULL, C. W., and PETTY, O. H.: Insulin resistance and sensitivity, *Jr. Lab. and Clin. Med.*, 1933, xviii, 1203-1211.
24. GOLDNER, M. G., and RICKETTS, H. T.: Insulin allergy, a report of eight cases with generalized symptoms, *Jr. Clin. Endocrinol.*, 1942, ii, 595-602.
25. HART, J. F., and VICENS, C. A.: Association of extreme insulin resistance with allergy. Report of a case, *Jr. Clin. Endocrinol.*, 1941, i, 399-401.
26. ALLAN, F. N., and SCHERER, L. R.: Insulin resistance due to allergy, *Am. Jr. Med. Sci.*, 1933, clxxxv, 815-821.
27. SHEPARDSON, H. C., GOBLE, G., and WITHROW, P. B.: Extreme insulin resistance in diabetes, *California and West. Med.*, 1944, lx, 201-204.
28. MARBLE, A., FERNALD, A. T., and SMITH, R. M.: Effect of human diabetic plasma upon blood sugar curves in rabbits following insulin, *Endocrinology*, 1940, xxvi, 735-742.
29. GLEN, A., and EATON, J. C.: Insulin antagonism, *Quart. Jr. Med.*, 1938, vii, 271-288.
30. WAYBURN, E., and BECKH, W.: Insulin resistance in diabetes mellitus, *Jr. Clin. Endocrinol.*, 1942, ii, 511-518.
31. LERMAN, J.: Insulin resistance—the rôle of immunity in its production, *Am. Jr. Med. Sci.*, 1944, ccvii, 354-360.
32. BANTING, F. G., FRANKS, W. R., and GAIRNS, S.: Anti-insulin activity of serum of insulin treated schizophrenic patient, *Am. Jr. Psychiatry*, 1938, xcv, 562-565.
33. RUSHTON, J. G.: Anti-insulin effect of blood plasma from certain diabetes mellitus patients, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 417-420.
34. BYWORTH, H. A.: Massive dosage with insulin, *Brit. Med. Jr.*, 1928, i, 801.
35. MOHLER, H. K., and GOLDBURGH, H. L.: Diabetes mellitus. With resistance to insulin and failure to obtain clinical improvement from its use, *Med. Clin. North Am.*, 1931, xv, 343-351.
36. WAYBURN, E.: Complete insulin resistance to diabetes, *Am. Jr. Med. Sci.*, 1935, cxc, 157-163.
37. ROOT, H. F., and RISEMAN, J. E. F.: The exceptional requirement of insulin and salt solution in diabetic coma, *Jr. Am. Med Assoc.*, 1938, cx, 1730-1732.
38. FELDER, L.: Insulin inhibition by serum of insulin resistant patient, *Jr. Clin. Endocrinol.*, 1946, vi, 339-345.
39. ALLAN, F. N., and CONSTAM, G. R.: Insulin resistance in a case of bronze diabetes, *Med. Clin. North Am.*, 1929, xii, 1677-1685.

40. WOOD, F. C., and FITZ-HUGH, T., JR.: Hemochromatosis in a metal worker, *Arch. Int. Med.*, 1929, xliv, 882-892.
41. ROOT, H. F.: Insulin resistance and bronze diabetes, *New England Jr. Med.*, 1929, cci, 201-206.
42. ROOT, H. F.: Acute hepatitis in a diabetic with severe acidosis and suppression of urine, *New England Jr. Med.*, 1935, ccxii, 545-547.
43. FALTA, W.: Insulin resistance in patient with cirrhosis, *Wien. Arch. Int. Med.*, 1938, xxxii, 97.
44. LAWRENCE, R. D.: Studies of an insulin resistant diabetic, *Quart. Jr. Med.*, 1928, xxi, 359-367.
45. BORDLEY, J., III: Disappearance of diabetes mellitus during the development of cirrhosis of the liver, *Bull. Johns Hopkins Hosp.*, 1930, lxvii, 113-122.
46. GLASS, W. I., SPINGARN, C. L., and POLLACK, H.: Unusually high insulin requirements in diabetes mellitus, *Arch. Int. Med.*, 1942, lxx, 221-235.
47. WIENER, H. J.: Diabetic coma requiring unprecedented amount of insulin, *Am. Jr. Med. Sci.*, 1938, clxvi, 211-217.
48. SCHLOSS, J. J.: Insulin resistance (with observations in an unusual case), *Ann. Int. Med.*, 1943, xix, 533-546.
49. CLAY, R. D., and LAWRENCE, R. D.: An insulin-resistant diabetic, *Brit. Med. Jr.*, 1935, i, 697-698.
50. REGAN, J. F., WESTRA, J. J., and WILDER, R. M.: Insulin resistance—report of a case, *New England Jr. Med.*, 1940, ccxxiii, 745-750.
51. JORDAN, W. R.: Insulin resistance: Report of two cases, *South. Med. and Surg.*, 1944, cvi, 361-363.
52. HELLER, C. G., and CHANDLER, R. E.: Gonadotropic hormone: Modification of the alcohol precipitation assay method, *Jr. Clin. Endocrinol.*, 1942, ii, 252-253.
53. MACALLUM, A. B., and SIVERTZ, C.: The potentiation of insulin by sulfones, *Canadian Chem. and Process Industries*, 1942, xxvi, 569.
54. GESSLER, C. J., HALSTED, J. A., and STETSON, R. P.: Effect of estrogenic substance on the blood sugar of female diabetics after the menopause, *Jr. Clin. Invest.*, 1939, xviii, 715-722.
55. SPIEGELMAN, A. R.: Influence of estrogen on insulin requirement of the diabetic, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 307-308.
56. GITLOW, S., and KURSCHNER, D. M.: Estrogen, diabetes and the menopause, *Arch. Int. Med.*, 1943, lxxii, 250-259.

# THE RELATIVE IMPORTANCE OF DIETARY SODIUM CHLORIDE AND WATER INTAKE IN CARDIAC EDEMA \*

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THE restriction of sodium chloride intake has been recognized for many years as essential in the treatment of cardiac edema. A diminished renal excretion of sodium and water is the primary factor in the production of edema according to Warren and Stead,<sup>1</sup> rather than increased venous pressure. Karrell's<sup>2</sup> once popular regimen of 800 c.c. of milk with no other food or fluid contained approximately 1.0 gm. of sodium chloride. In many hospitals at the present time, the "cardiac general" diet restricts the sodium chloride intake to a minimum of 3.0 gm. and customarily fluids are limited to 1500 c.c. daily. However, several investigators including Schroeder,<sup>3</sup> Schemm,<sup>4, 5</sup> Bridges, Wheeler, and White,<sup>6, 7</sup> and Leevy, Strazza, and Jaffin,<sup>8</sup> have recommended on the basis of clinical investigations that the sodium intake be restricted even more rigidly, and under these conditions beneficial results were obtained without restriction of water intake.

Schemm<sup>5</sup> attacked, as Schroeder did three years earlier, the accepted method of restricting fluids in the treatment of cardiac edema. He used a diet containing less than 2.0 gm. of sodium chloride and actually forced fluids to 5000 c.c. and over in his patients with apparently good results. Others,<sup>6, 8</sup> while obtaining favorable results with a free fluid intake, have not stated that they found any definite advantage accruing from forced fluids, as judged by purely clinical observation. The question as to whether water encouraged to moderate intake levels or water forced to high intake levels produces an increased loss of edema fluid (as claimed by Schemm) has not been settled. We studied this aspect of the problem.

## METHOD OF INVESTIGATION

**Diet.** Twenty-two patients with edema of congestive heart failure were investigated on a low salt diet of less than 1.0 gm.\* of sodium chloride (14 m.eq. of sodium) and an additional eight patients were studied on the hospital cardiac general diet of 3.0 gm. (51 m.eq. of sodium). Sample one-day

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\* The use of salt-free bread is essential; two analyses of ordinary bread showed 4.9 m.eq. of sodium per slice. Neo-curtasal (Winthrop Chemical Co.) has in some cases been helpful as a salt substitute after patients left the hospital. This product contains no sodium.

diets were analyzed periodically for their total sodium content, and some of these analyses included all medicines the patient received during that 24 hour period. The diet used was acid-ash, although our paramount aim was a total sodium content of under one gram.

*Fluids.* The fluid intake was frequently altered. Daily fluid intakes varied from 1000 c.c. to 7500 c.c. in different patients on different days. When encouraged to do so, most patients took an average of 3000 c.c. daily. Some were on fluids restricted below 1500 c.c. throughout the first week of treatment, others were forced to over 4000 c.c., while still others were restricted during the first three days of treatment and forced during the sub-

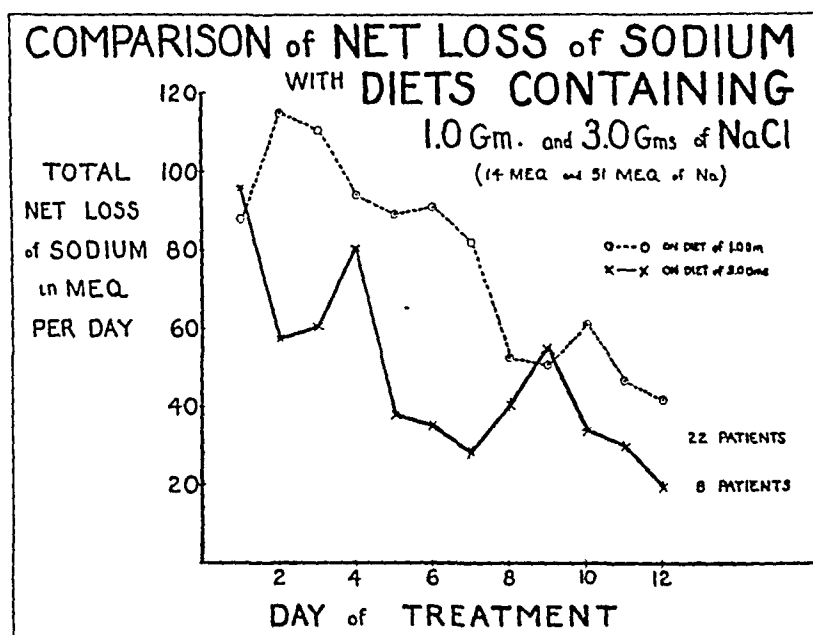


FIG. 1. Comparison of the net loss of sodium with diets containing less than 1.0 gm. and 3.0 gm. of sodium chloride (14 and 51 m.eq. of sodium respectively).

sequent four days and vice versa. These varying intakes were employed during the first seven days because, as shown below, the maximum sodium excretion occurred during the first week of the regimen. After the first week fluids were allowed as desired.

*Determinations.* Serum sodium and chloride levels and the carbon dioxide combining power were determined twice weekly on most patients. Twenty-four hour urines were collected daily and the total sodium ascertained by means of the flame photometer. Daily urine chloride was also determined.

*Medications.* All medicines known to contain appreciable amounts of sodium were avoided. No mercurial diuretics were used in any of the reported results (figures 1 and 2) either during or for at least two weeks before treatment was begun so that the effect of diet and fluids on sodium excretion could better be evaluated. Some of the cases did receive am-

monium chloride or ammonium sulfate. All patients were fully digitalized at least 36 hours before the regimen was started except for four who did not receive digitalis until the edema had subsided. All had congestive heart failure with clinical evidences of edema.

## RESULTS

*Sodium Intake and Excretion.* Daily determinations of the 24 hour urinary output of sodium were averaged irrespective of fluid intake for each of the two dietary regimens. The net loss of sodium was calculated by subtracting the dietary intake from the 24 hour urinary excretion and adding

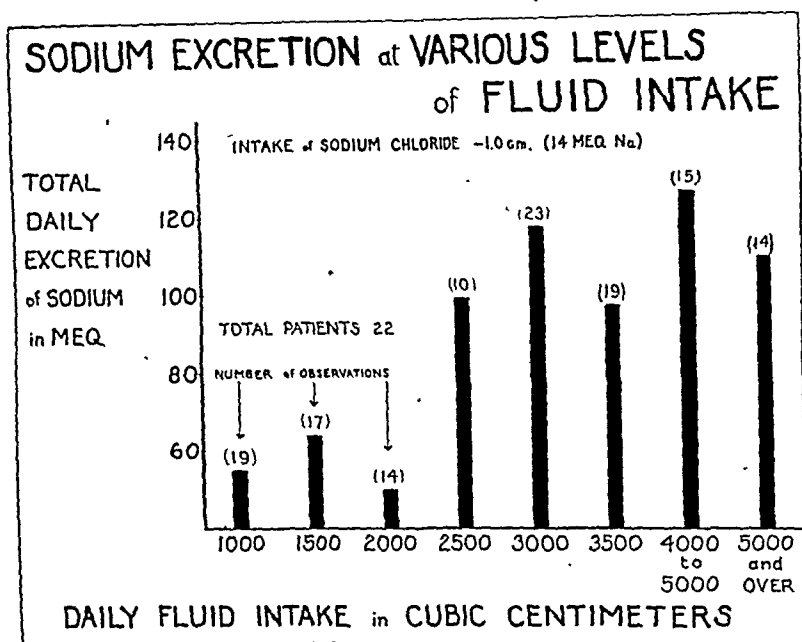


FIG. 2. Total daily sodium excretion at various levels of fluid intake.

20 m.eq. allowed for skin and fecal loss (see below). In general, chloride excretion paralleled that of sodium, but the chloride intake was not determined. A comparison of the two diets (figure 1) shows that the net loss of sodium on the diet of less than 1.0 gm. of sodium chloride is appreciably greater than on the diet of 3.0 gm. The maximum sodium loss is achieved during the first seven days of treatment, and after this period a moiety is excreted at a relatively constant rate. Particularly on the 1.0 gm. diet (actually 14 m.eq. of sodium), the excretion rate of sodium seems more closely related to its load in the body at the time when the low salt intake regimen is begun. Fluid intakes varied at random for any particular day of treatment so that the decreasing sodium loss can not be attributed to a decreasing fluid intake.

*Total Fluid Intake and Sodium Excretion.* Average 24 hour sodium excretions at various levels of fluid intake were calculated for those cases on



the diet containing less than 1.0 gm. of sodium (figure 2). Only values obtained during the first seven days are included. The total sodium excretion on a daily fluid intake of 1500 and 2000 c.c. was only about half that which occurred when the fluid intake was 3000 c.c. The difference was shown to be statistically significant.

*Clinical Results.* Very satisfactory clinical improvement was noted in the majority of our 22 patients treated with the less than 1.0 gm. sodium chloride diet. Seven cases showed an excellent response with rapid clearing of large amounts of edema, as illustrated by Case 1 (figure 3). Ten cases

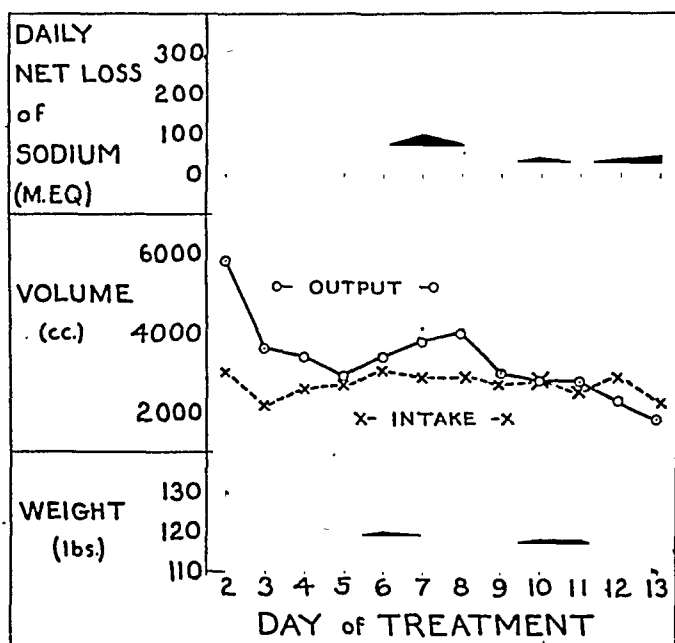


FIG. 3. (Case 1) Rapid loss of edema with the less than 1.0 gm. sodium chloride diet and moderate fluid intake.

showed slower but satisfactory clearing of edema. In five cases maintained four to 15 days on the less than 1.0 gm. sodium chloride diet there was no apparent clinical improvement (Case 2, figure 4).

The majority promptly lost an average of  $1\frac{1}{2}$  lbs. per day. Some showed a urinary output actually exceeding the water intake. Most cases had a negative water balance even when the urine output was less than the water intake, reflecting extrarenal water loss of approximately 1000 c.c. per day. These effects were achieved without recourse to mercurial diuretics. Clinical evidences of edema disappeared usually within one week.

No adverse effects were noted which could be directly attributed to the ingestion of extra water. However, five of the patients with chronic edema of long standing responded very poorly to the diet and ingestion of water alone. In these cases it was felt that the use of mercurial diuretics was mandatory. None of these patients seemed to show increased edema before administration of mercurial diuretics. Three of these patients slowly im-

proved. One with hypertensive heart disease died in uremia after 17 days' treatment. Another with arteriosclerotic heart disease and congestive failure died of far advanced active pulmonary tuberculosis.

## ILLUSTRATIVE CASE REPORTS

*Case 1.* (Figure 3) E. E., a 62 year old white male, admitted for the fourth time during the past six years with congestive failure due to hypertensive arteriosclerotic heart disease. He had discontinued digitalis therapy one month before admission. Physical findings included the liver edge palpable 8 cm. below the right costal margin. There were 3+ pitting edema of both lower legs and small pleural

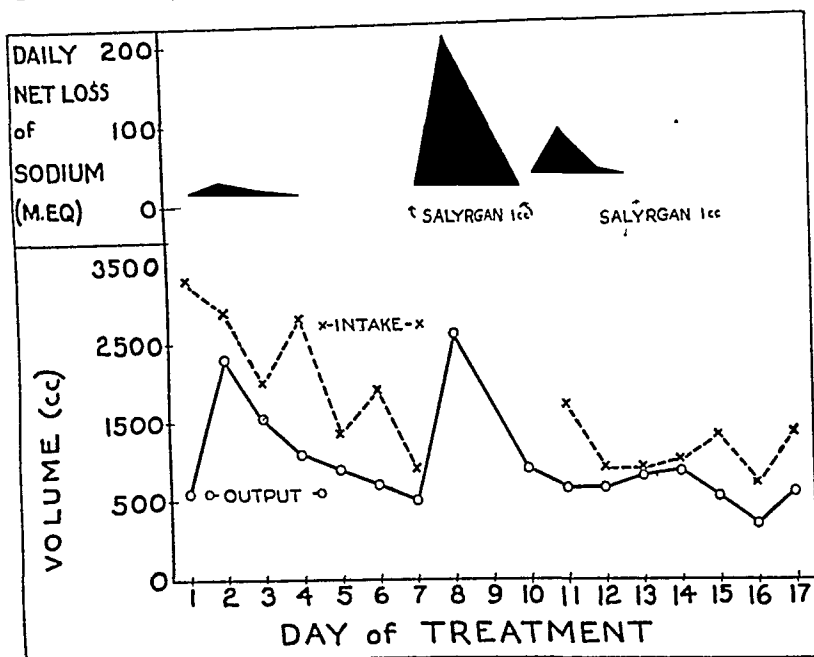


FIG. 4. (Case 2) No clinical improvement with the less than 1.0 gm. sodium chloride diet and a low fluid intake.

effusions bilaterally. Digitalization was carried out on admission and two days later the regimen was begun. On the less than 1.0 gm. sodium chloride diet and a moderate fluid intake he improved rapidly and was free of visible edema within one week. The response of urinary output greater than the corresponding fluid intake was unusual and occurred in only seven of our patients.

*Case 2.* (Figure 4) D. D., a 36 year old white woman, admitted for the fourth time during the past three years with congestive heart failure. She had had rheumatic heart disease since age eleven. No digitalis had been taken recently. Physical findings included the liver margin 6 cm. below the right costal margin, mild ascites, and 3+ pitting edema of both lower legs and sacrum. Blood pressure was 210 mm. Hg systolic and 100 diastolic. Phenolsulfonphthalein excretion test 65 per cent after two hours. She was promptly digitalized on admission and the regimen begun two days later.

*Comment.* This patient was so weak that she could not be weighed and no clinical improvement was manifest after one week of treatment. Mercurial diuretics were subsequently employed but even then her response was

very slow and she still had some edema two weeks after admission. Improvement finally warranted discharge after 32 days of hospitalization.

Despite such low sodium excretions as the occasional values of 2 m.eq. for a 24 hour period, this patient probably had a negative sodium balance resulting from extrarenal losses of the order of 20 m.eq.<sup>9, 10, 11</sup> and a dietary intake of 14 m.eq. of sodium per day. The daily fluid intakes were low, but the patient's distressing symptoms of congestive failure precluded the ingestion of more water. At the estimated rate of a daily net loss of 8 m.eq. of sodium (only 2 m.eq. in the urine) many days would have elapsed before any appreciable loss of sodium had occurred. Under these circumstances even increasing the fluid intake to double the urine volume would only have increased the sodium excretion by about 2 m.eq. more per day.

### DISCUSSION

In general the clinical responses of our patients seemed to depend on their ability to excrete sodium. Where the sodium chloride excretion was very low, the patients responded poorly. Although forcing fluids caused some increase in sodium and water loss, the slightly negative sodium balance was seemingly not enough to affect the clinical course. However, in none was there any adverse effect from the ingestion of copious amounts of water when the diet was kept low in sodium.

In some patients the concentration of sodium in the urine was higher than in those mentioned above.\* An increase of urinary volume following an increased water intake resulted in a corresponding increase of total sodium excretion. In these cases large water intakes were of much value in augmenting the sodium loss.

This regimen is not considered a substitute for mercurial diuretics, especially in the more refractory cases. The relative sodium loss of three to five days on the regimen for the average patient was only the equivalent of that obtained by 1 c.c. of Salyrgan. Nevertheless, the low sodium diet and moderate intake of water (3000 c.c. daily) appear to be most valuable adjuncts to digitalis and the mercurials in the treatment of cardiac failure.

*The Theory of the Regimen.* Cardiac edema is associated with certain aberrations in renal function. This disturbance in renal function is manifested preëminently by the inability of the kidney to eliminate sodium and chloride in the same manner as the normal kidney. This is correlated with the lack of concentrating power for these ions, as noted by Futcher and Schroeder<sup>12</sup> for chloride and by us for sodium. There is no evidence that the ability to dilute these ions in the urine well below plasma levels is significantly different from normal. This relatively normal diluting ability of the kidney in cardiac edema may be used to evaluate the importance of low salt and high water intake in relieving cardiac edema.

\* Before the regimen was begun the urinary sodium concentration was rarely as high or higher than the serum concentration. This observation parallels that of Futcher and Schroeder<sup>12</sup> on chlorides.

A quantitative theoretical basis for the dehydrating action of water in normal man has been discussed by Wolf.<sup>13, 14, 15</sup> It was shown that when a salt: water intake (as a solution) is steadily maintained below about 15 to 20 m.eq./l there is a renal leakage of salt in excess of intake. This critical concentration was called the minimal isorrheic concentration or MIC. But the normal plasma levels of sodium and chloride are protected. More water is excreted than is taken in and this steady dehydration prevents a fall in electrolyte concentration which would otherwise occur as a salt deficit developed. It is considered a tenable hypothesis that this mechanism operates in the cardiac patient.

The experience of others as well as our own has established that with diets containing 3 to 4 grams of salt no appreciable loss of edema follows the administration of moderate or fairly high water intakes. We may consider a case of a daily salt intake of 68 m.eq. (4 grams) and a water intake of 3 liters. The extrarenal salt loss is taken as 20 m.eq. per day.\* Thus the ratio of *dietary salt* increment to the *dietary water* increment offered to the kidney is

$$\frac{\text{salt}}{\text{water}} = \frac{68 - 20}{3} = \frac{48}{3} = 16 \text{ m.eq./l.} \quad (1)$$

This ratio, which would characterize the total daily salt and water intake if they were taken as a solution, may be called the "effective intake concentration" of salt (sodium).

Since cardiacs ordinarily maintain essentially normal or constant plasma concentrations of sodium and chloride and since they seem to be in water balance at the edema level when the effective intake concentration is approximately equal to the normal MIC as above, it would appear that a MIC in the cardiac can be of the same magnitude as that of the normal.

On a 2 gram diet (34 m.eq.) with the same water intake as above, we would have

$$\frac{\text{salt}}{\text{water}} = \frac{34 - 20}{3} = \frac{14}{3} = 4.7 \text{ m.eq./l.} \quad (2)$$

This effective intake concentration, being considerably lower than the MIC, is conducive to the removal of edema. If the cardiac behaves as the normal with regard to this principle of dehydration (figure 1 shows how the leakage of sodium increases as the effective intake concentration is lowered), then still lower salt intakes providing lower effective intake concentrations of salt should remove edema more readily.†

\* The quantity of preformed and oxidative water of the food is approximately offset by the extrarenal water loss; they are omitted for simplicity.

† In practice our salt intakes of 14 m.eq. per day provided effective intake concentrations of salt of zero, or even negative values. The results attest to the advantage of such low values.

If the 4 gram diet above were to be complemented with sufficient water to give an effective intake concentration of 4.7 m.eq./l as in the 2 gram diet of equation (2) then

$$\frac{\text{salt}}{\text{water}} = \frac{68 - 20}{10.2} = \frac{48}{10.2} = 4.7 \text{ m.eq./l.} \quad (3)$$

That is, over 10 liters per day would theoretically be required to offset the extra salt.\* Practically this fluid intake is almost impossible to attain and experience shows it is undesirable. These computations indicate that low salt intake is relatively more effective than high water intake in this treatment of edema; and that the key to successful treatment is not the low salt or the high water per se. Rather the basic mechanism of the therapy is a low effective intake ratio of salt to water. This is more easily obtained in practice by lowering salt intake than by raising water intake. The degree to which the latter can be carried out falls short of theoretical requirements when salt intake is not sufficiently restricted.

#### SUMMARY AND CONCLUSIONS

On a diet containing less than 1 gm. of sodium chloride daily 22 patients with edema of congestive heart failure were investigated and an additional eight patients were studied on the hospital cardiac general diet containing 3.0 gm. of sodium chloride. Total daily urinary sodium and chloride excretions were observed with varying fluid intakes.

1. From these studies it was believed that the net loss of sodium and of edema in patients with cardiac failure is greater when a diet containing less than 1.0 gm. rather than 3.0 gm. of sodium chloride is used.

2. The net loss of sodium and of edema is also greater when patients are encouraged to take 3000 c.c. of fluid daily rather than be restricted to the customary 1500 c.c. There seems to be little added benefit from attempting to force fluids above 3000 c.c.

3. It is suggested theoretically that the fundamental object of the regimen described to treat cardiac edema is the maintenance of a low ratio of sodium intake to water intake rather than a low sodium or a high water intake per se. This concept provides a basis for evaluation of the relative importance of dietary salt and water in this regimen; and it accounts quantitatively for the fact that restriction of salt to low intakes is more readily effective in relieving cardiac edema than forcing fluid to very high levels.

\* The same effective salt: water intake concentration at two different rates of water intake does not imply the same rate of dehydration. The theoretically higher rate of dehydration at higher water intakes varies with the salt intake.<sup>14</sup> It is often insignificant as said earlier. For each extra gram of salt added to the diet it may be estimated that from one to several liters of extra water would have to be added to maintain the same rate of dehydration in the edema patient. But this computation cannot be made at all accurately because of the changing character of salt excretion as the patient proceeds to reduce his edema salt load.

## BIBLIOGRAPHY

1. WARREN, J. V., and STEAD, E. A., JR.: Fluid dynamics in chronic congestive heart failure, *Arch. Int. Med.*, 1944, lxxiii, 138-147.
2. KARRELL, PHILPPE: De la cure de lait, *Arch. gen. de med.*, 1866, Vol. 128, O. S., Series 6, Vol. 8, 513-533.
3. SCHROEDER, H. A.: Studies on congestive heart failure. I. The importance of restriction of salt as compared to water, *Am. Heart Jr.*, 1941, xxii, 141-153.
4. SCHEMM, F. R.: A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the regime, *Ann. Int. Med.*, 1942, xvii, 952-969.
5. SCHEMM, F. R.: A high fluid intake in the management of edema, especially cardiac edema. II. Clinical observations and data, *Ann. Int. Med.*, 1944, xxi, 937-976.
6. BRIDGES, W. C., WHEELER, E. O., and WHITE, P. D.: Low-sodium diet and free fluid intake in the treatment of congestive heart failure, *New Eng. Jr. Med.*, 1946, ccxxxiv, 573-578.
7. WHEELER, E. O., BRIDGES, W. C., and WHITE, P. D.: Diet low in salt (sodium) in congestive heart failure, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 16-20.
8. LEEVY, C. M., STRAZZA, J. A., and JAFFIN, A. E.: Fluids in congestive heart failure, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 1120-1125.
9. FREYBERG, R. H., and GRANT, R. L.: Loss of minerals through the skin of normal humans when sweating is avoided, *Jr. Clin. Invest.*, 1937, xvi, 729.
10. KEUTMANN, E. H., BASSETT, S. H., and WARREN, S. L.: Electrolyte balances during artificial fever with special reference to loss through the skin, *Jr. Clin. Invest.*, 1939, xviii, 239.
11. MACKAY, E. M., and BUTLER, A. M.: Studies of sodium and potassium metabolism. The effect of potassium on the sodium and water balances in normal subjects and patients with Bright's disease, *Jr. Clin. Invest.*, 1935, xiv, 923.
12. FUTCHER, P. H., and SCHROEDER, H. A.: Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride, *Am. Jr. Med. Sci.*, 1942, cciv, 52.
13. WOLF, A. V.: The dehydrating effect of continuously administered water, *Am. Jr. Physiol.*, 1945, cxliii, 567.
14. WOLF, A. V.: The retention and excretion of continuously administered salt solutions, *ibid.*, cxliii, 572.
15. WOLF, A. V.: Renal regulation of water and some electrolytes in man, with special reference to their relative retention and excretion, *ibid.*, cxlviii, 54.

# THE PROGNOSIS OF SYPHILITIC AORTIC INSUFFICIENCY \*

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THE course of syphilitic aortic insufficiency is generally believed to be rapidly progressive.<sup>1, 2, 3, 4, 5, 6</sup> Death from cardiac failure is said to occur 12 to 36 months after the discovery of the lesion,<sup>7</sup> although Grant<sup>8</sup> in a study of 1,000 cardiac patients showed that the 10-year case fatality rate of syphilis of the aortic valve is only 64 per cent. It has been reported that anti-syphilitic therapy doubles the life expectancy in this disease.<sup>3</sup>

In a previous study from this clinic<sup>9</sup> of a large group of patients with aortic valvular syphilis, it was observed that current prognostic data based on the course of the disease following the onset of symptoms of failure were inapplicable, as the disease is characterized by an asymptomatic phase of two to 10 years' duration. The present study represents a continued investigation and follow-up of these same patients.

In the earlier study, a group of 91 patients with syphilitic aortic insufficiency was followed, and the period of observation, presenting complaint, and ability of these patients to work were determined. They were classified into three groups according to whether they were asymptomatic (I), had symptoms on questioning only (II), or were symptomatic (III). Patients in Group I denied any exertional or paroxysmal dyspnea, cough, palpitations, substernal or precordial pain, orthopnea, or ankle edema. Those in Group III presented one or more of these symptoms, most commonly exertional dyspnea. The Group II patients had not sought medical attention for these symptoms, but acknowledged one or more of them after specific questioning. Forty-seven of these 91 patients were available for determinations of circulation time, venous pressure, vital capacity, cardiothoracic ratio, and blood pressure. It was found that, in the group studied, aortic insufficiency due to syphilis was present in a clinically recognizable form for two to 10 years before the development of symptoms. The asymptomatic phase was encountered in approximately one-half of the patients with valvular syphilis.

*Materials and Methods.* In the present investigation, 27 of the 47 patients previously studied were available for a repetition of the observations carried out five and one-half years previously. Three additional patients were known to be alive, but could not be located at the time clinical deter-

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minations were repeated. Thirteen had died, and reliable information as to the circumstances of their deaths was obtained. Autopsies were performed in three of the 13 cases, and the diagnosis of syphilitic aortic insufficiency was confirmed in all three. Determinations of circulation time,<sup>10</sup> venous pressure, vital capacity, blood pressure, and heart width were repeated on each of the 27 patients available for these studies in the same manner as they had been performed previously, with two variations. Calcium gluconate was used for arm-to-tongue time in a few patients because decholin was not available. There is no significant difference in the circulation time as tested by these two materials.<sup>11</sup> Estimated heart width calculated by means of Ungeleider's tables<sup>12</sup> was substituted for the cardiothoracic ratio. These findings are presented in table 3.

The diagnosis of syphilitic aortic insufficiency was made by demonstrating the presence of a diastolic murmur over the aortic area, and/or down the left sternal border, in a patient known to have had syphilis and who had no evidence of mitral stenosis or congenital heart disease either clinically or by roentgen-ray. The murmur was confirmed by at least two different observers, and patients were separated into two groups according to the quality of the diastolic murmur. When the murmur was easily audible in the recumbent position, it was called "loud." When it could be heard only by having the patient sit up, lean forward, and hold his breath in expiration, it was called "soft."

Roentgenograms of the chest were obtained on each of the 27 patients to determine heart size and aortic width as compared with heart size and aortic width noted in the earlier study. The width of the ascending aorta was determined by measuring the ascending aortic shadow on a left anterior oblique or left lateral chest roentgen-ray film. Four centimeters was accepted as the upper limit of normal width. The width of the heart was measured as the greatest transverse cardiac diameter on a two-meter roentgen-ray plate.

Classification of patients into the three groups according to symptoms was retained, and the individual patients were reassigned accordingly to their present symptomatology, as in table 5. Patients were also tabulated (table 4) according to their ability to work at the time of the original survey and again at the time of the present study, five and one-half years later. Period of observation, duration of asymptomatic phase, duration of life after onset of symptoms, age, sex, and color are recorded in table 1.

*Observations.* Forty-three patients were followed for two to 16 years. At the time of the present study, 30 of these were alive. The group as a whole were doing remarkably well, even though the presence of aortic insufficiency had been recognized six to 12 years previously. The asymptomatic phase of the disease in this group lasted two to 10 years, and the duration of the symptomatic phase of the disease was even longer, two to 14 years. In the five and one-half years of the investigation, the status of 20



TABLE I

Name	Age	Race	Sex	Years of Observation	Asymptomatic Phase, Years	Symptomatic Phase, Years	Years Alive after Diagnosis	Age at Death
Group I								
BJ	43	W	F	5	5		5	
JF	68	B	F	7	6	1	6	
SM	60	W	F	8	2	5	7	
EG	59	W	F	10	6		6	
HJ	63	B	F	6	6	1	6	
JM	50	W	M	10	10		10	
BA	59	W	F	10	10		10	
MZ	69	W	M	11	5	2	7	
DF	63	W	F	7	7		7	
SK	60	W	M	7	6		6	
JE	77	B	M	9	7	2	9	
MMc	77	W	F	11	6	5	11	
MG	64	W	M	9	7		7	
MF	45	W	F	7	7		7	
MD	47	W	M	6	6		6	
MV	62	W	M	10	10		10	
CK	51	W	M	4	4		4	
BF		W	F	6	0	3	3	46
AW		W	M	8	8		8	63
HM		W	M	8	8		8	81
Group II								
GF	54	W	F	7	7		7	
FW	75	W	F	9	?	9	9	
LL	77	W	M	16	0	6	6	
FK	61	W	M	8	3	5	8	
HJ		W	M	5	5		5	64
JB		W	M	3	?	3	3	60
JMc		W	M	4	?	4	4	73
Group III								
RK	48	W	F	7	0	6	6	
JG	53	W	M	11	?	11	11	
AC	57	W	F	9	0	7	7	
AM	60	W	F	8	2	7	8	
MB	71	W	M	8	0	7	7	
JH	35	B	F	8	?	8	8	
GW	50	W	F	7	?	7	7	
WW	49	W	M	8	?	14	8	
SW	60	W	M	12	?	12	12	
CB		W	M	5	?	5	5	71
GL		W	M	2	?	2	2	60
JK		W	M	3	2	2	3	77
JMc		W	M	4	?	4	4	67
JP		W	M	5	?	5	5	42
FN		W	M	2	?	7	2	69
NM		W	M	2	?	3	2	55
Range:				2-16	2-10	2-14	2-12	42-81
Average:				7.2 yrs.	6.0 yrs.	5.6 yrs.	6.5 yrs.	63.4 yrs.

of the 43 patients had changed. Only six of the group previously reported as asymptomatic have developed symptoms in the interval. Thirteen of the whole group have died, and seven had to be reclassified as symptomatic-questioning or frankly symptomatic.

TABLE II

Group	Follow-up in Years	No. of Patients	Living	Died of Heart Disease	Died of Other Cause
I (Asymptomatic)	6-12	21	18	1	2
II (Symptoms on Question Only)	5-16	6	3	1	2
III (Symptomatic)	2-12	16	9	6	1
Total	2-16	43	30	8	5

In table 3 may be seen a comparison of the data concerning cardiac efficiency obtained in the present study and the values noted five and one-half years previously. A significant elevation in the circulation time above normal was noted in 12 patients, and the highest value was 26 seconds. In the present study, the venous pressure determinations were elevated in 14 patients, whereas previously all but one were within normal limits. The vital capacities were below 70 per cent of normal in 13 patients. Previously, eight were below 70 per cent. Twelve patients had widening of the ascending aortic shadow, two having developed this in the previous five and one-half years. Eight of the patients presented a combination of two or more of these positive findings, thus showing a correlation among the various indices.

A striking feature of almost all these patients was their ability to continue their usual pursuits; and, with one exception, all were well-compensated despite their age and the duration of their known aortic insufficiency (6 to 12 years). Indeed, one who was unable to work at the time of the previous evaluation has become asymptomatic and able to work as a switchboard operator 30 hours a week. This has been tabulated in table 4.

Of the 27 living patients, 12 have remained completely asymptomatic. These work as: a janitor for a 48-family apartment building, a full-time waiter, a chauffeur, a machine operator, a furrier, a cook and a housewife. Two patients who were originally classified as asymptomatic have been placed in Group II; one is confined to a mental institution, and the other is a janitor for an apartment house. Four of the patients in the original Group I are now in Group III, but they are doing approximately the same amount of work as they did five and one-half years previously. All these latter patients are in the seventh and eighth decades of life. The one patient in Group II who has been placed in Group III is 75 years old and unable to work. In 1941 she did housework. Thirteen of the original group of 43 patients have died, eight of them because of heart failure. The average age

TABLE III  
 Determinations of Cardiac Efficiency  
 (Upper figure, 1941 study; lower figure, 1946)

Name	Circulation Time	Venous Pressure	Vital Capacity	Per Cent Normal	Blood Pressure	Pulse Rate	Aortic Widening	Heart Width	Estimated Heart Width	Quality of Diastolic Murmur
Group I										
BJ	10.2	79	2350	78	150/85	116	0	112	118	soft
	11.8	197	2300	78	160/80	90	0	110	121	
JF	10.7	60	2000	74	160/80	100	0	102	106	soft
	13.0	150	1900	70	200/90	88	0	108	107	
SM	11.4		2700	74	140/80	72	0	120	121	soft
	19.5	175	2200	70	130/80	80	0	120	128	
EG	12.0	100	2300	80	150/70	64	0	124	124	soft
	15.0	105	2100	70	140/78	62	0	125	125	
HJ	12.1	50	2000	74	170/90	88	+	130	121	loud
	13.5	107	1800	68	190/80	66	+	131	119	
JM	12.5	70	3800	90	180/90	84				loud
	19.0	180	3200	69	240/110	84	+	150	132	
BA	14.0	90	2800	80	190/54	80	+	155	140	loud
	16.5	215	2300	66	250/80	72	+	183	145	
MZ	15.8	115	2500	60	190/80	76				loud
	23.0	120	2000	48	220/88	68	+	170	129	
DF	16.9	44	1900	54	190/90	112	0	150	139	loud
	14.5	100	1800	50	220/80	92	0	160	145	
SK	17.3	88	3400	89	140/70	66		145	119	soft
	18.5	95	3400	89	156/70	60	+	130	115	
JE	18.1	51	3350	80	170/90	74	0	110	113	soft
	23.0	81	3200	77	172/88	74	0	115	113	
MMc	18.4	88	1400	38	162/82	90	+	150	153	soft
	25.0	105			150/75	82				
MG	18.5	70	2200	55	180/90	68	0	139	118	soft
	22.0	60	2000	50	178/88	72	0	140	120	
MF	11.0	70	2400	70	150/82	84	0	130	132	soft
	15.0	155	2900		160/90	88	0	130	140	
MV	17.0	68	2900	62	125/60			140	132	soft
	17.0	170	3000	67	150/70	72		145	134	
MD	14.5	94	3500	80	130/60	100		115	120	loud
	14.0	130			150/50	98				

TABLE III—Continued

Name	Circulation Time	Venous Pressure	Vital Capacity	Per Cent Normal	Blood Pressure	Pulse Rate	Aortic Widening	Heart Width	Estimated Heart Width	Quality of Diastolic Murmur
Group II										
GF	12.7 17.0	110	2000 1800	70 61	188/86 160/60	96 90	0 0	104 105	118 115	soft
FW	14.4 25.0	78 130	1600 1600	45 45	214/78 220/70	72 76	++	150 135	148 123	loud
LL	15.6 24.0	50 98	2700 2100	78 50	208/80 230/80	 72	0 +	133 158	130 130	loud
Group III										
RK	14.1 17.5	102 175	2700 2300	90 74	180/90 210/100	116 84	0 0	105 110	112 116	none?
JG	14.7 26.0	85 85	2800 2200	63 51	160/60 140/40	88 96	0 +	160 167	122 123	loud
AC	14.9 27.0	82 172	2300 2200	81 71	180/60 230/50	80 70	++	132 150	122 122	loud
AM	16.3 18.0	99 192	1750 1400	58 50	212/110 228/100	96 90	0 0	135 138	142 136	soft
MB	16.6 23.0	97 200	2600 2200	53 44	145/60 172/60	88 88	++	170 184	142 146	soft
JH	17.9 17.0	130 172	2000 2000	76 76	158/32 186/40	84 82	++	148 155	111 107	loud
GW	22.5 17.5	50 70	2000 2000	70 70	170/45 138/42	100 72	0 0	133 117	112 112	loud
WW	15.0 23.5	90 190	2200	46	140/50 156/74	92 90	 +	147 148	133 133	loud
Group IV (dead)										
BF	13.9	95	2000	66	270/145	92	+	135	127	soft
AW	15.0	92	3150	85	168/64	72	+	146	136	loud
HM	16.6	80	2400	56	210/70	88				loud
HJ	13.6	37	2500	75	135/60	118	0	120	121	soft
JB	22.4	65	3100	76	170/65	80	0	160	136	loud
JMc	29.8	135	1850	42	200/65	72	+	175	134	soft
CB	14.5	98	2000	45	190/70	80	0	140	125	soft
GL	19.7	86	2700	72	150/40	80	+	154	110	loud
JK	22.8	117	2500	56	165/50	80				loud
JMc	23.8	82	2400	59	220/90	52	+	190	125	loud
JP	24.6	72	2500	64	194/50	80	0	173	133	loud
FN	28.2	52	2000	41	140/70	64	+	168	138	loud
NM	28.8	53	3000	65	170/15	112	+	182	128	loud

at death was 63.4 years, an average of 4.4 years (one to seven years) after the diagnosis of aortic insufficiency was made.

Examination of table 6 shows that among all the living patients, aortic insufficiency has been recognized for an average of 7.6 years (5 to 12 years). There is no marked difference among the three groups as to the time their aortic insufficiency was discovered.

TABLE IV  
(Upper figure 1941; lower, 1946)

Name	Age	Type of Work	Hours per Day
Group I			
BJ	43	Nursemaid for two small children Machine operator, biscuit factory	Full-time 8
JF	68	Apt. house supt. and housework for 2 Apt. house supt. and housework for 2	9
SM	60	Sewing (also helps with housework) Sewing (also helps with housework)	6
EG	59	Housework for two Furrier	7
HJ	63	Nursemaid (four children) Housework for self (3½ rooms)	Full-time
JM	50	Chauffeur Chauffeur	Full-time
BA	59	Cigar maker (2 days a week, own housework) Own housework	10
MZ	69	Salesman Unemployed—able to work	5-6
DF	63	Housework for self and four others Housework for self and four others	
SK	60	Janitor for 44-family building Janitor for 48-family building	15 16
JE	77	Unemployed—able to work Unemployed—able to work	
MMc	77	Housework Confined to mental hospital, ambulatory	
MG	64	Waiter Waiter	8 8
MF	47	Cook Cook	6-8 8
MD	46	Taxi driver Truck driver	8 8
MV	62	Carpenter Cabinet maker	8 12

TABLE IV—*Continued*

Name	Age	Type of Work	Hours per Day
Group II			
FW	75	Housewife—housework for two Unable to work	
LL	77	Waiter Waiter	6 5
Group III			
RK	48	Housework for three Housework for three	
JG	53	Unemployed—able to work Boatswain	7
AC	57	Housewife—housework for two Housewife—housework for two	
AM	60	Housewife—housework for two Housewife—housework for two	
MB	71	Bartender Bartender	9/week 8
JH	35	Housewife—housework for two Housewife—housework for two	
GW	50	Unable to work Switchboard operator	4
WW	49	Salesman Salesman	4 8
Group IV (dead)			
BF	46	Head matron, department store	8
AW	63	Unemployed—able to work	
HM	81	Salesman	
HJ	64	Decorator	?
JB	60	Unemployed—paresis	7
JMc	73	Unemployed—osteomyelitis	
CB	71	Housework—one room	
GL	60	Actor—unable to work	
JK	73		
JMc	67	Unable to work	6-8
JP	42		
FN	69	Unable to work	2-3
NM	55	Unable to work	

Table 7 illustrates the age distribution of those who died directly because of their heart disease.

Nine of the symptomatic patients, groups II and III, have been maintained on digitalis with improvement in compensation for two to six years. Of the 13 who died, nine were digitalized, all for at least two years, and one

TABLE V  
Changes in Classification of Patients

Group	February 1941	January 1947			
		Group I	Group II	Group III	Dead
I	21	12	2	4	3
II	6	—	2	1	3
III	16	—	—	9	7
Total	43	12	4	14	13

TABLE VI  
Patients Living, January 1947

Group	No. of Patients	White		Colored		Ages	Average Age	Average Years Aortic Insufficiency Known
		Male	Female	Male	Female			
I	17	7	7	1	2	43-77	62.5	7.3 (5-11)
II	4	2	2	0	0	54-77	68.7	7.5 (6-9)
III	9	4	4	0	1	35-71	53.4	8.2 (6-12)
Total	30	13	15	1	3	35-77	58.9	7.6 (5-12)

TABLE VII  
Patients Dead of Heart Disease, January 1947

Group	No. of Patients	Ages at Death	Average Age	Years Aortic Insufficiency Known
I	1	81	81	8
II	1	60	60	5
III	6	42-73	62.8	2-8
Total	8*	82-81	63.1	2-8

\* All were white males.

for five years. In all the cases that died in failure, the heart size was markedly increased. All but three patients who died were in the seventh and eighth decades.

## DISCUSSION

In the previous study from this clinic, it appeared that the length of the asymptomatic phase might be measured in years rather than months. The present study confirms the assumption that the asymptomatic phase of this valvular disease is measured in years (two to 10, average six years), and that even after the onset of the symptomatic phase the patients may maintain compensation, continue to work, and live two to 14 years (average 5.6 years).

The data presented in this study represent the survival time from the discovery of the aortic insufficiency to the time of death, or to the time the study was terminated. It is reasonable to assume that in many patients the aortic insufficiency was unrecognized for months, perhaps years. In 32 of the series, the diagnosis was established at the time of the first visit to the clinic. Moreover, at the completion of the study, 30 (70 per cent) of the patients were still alive and in apparent good health, 12 (28 per cent) completely asymptomatic.

It is difficult to evaluate the factors responsible for the more favorable outlook in this series as compared to those previously reported by others.<sup>5, 13</sup> Some authors have suggested that heavy labor is detrimental; others say that sex and race play an important rôle. It is frequently stated that Negro males present the poorest prognosis.<sup>13</sup> It should be noted, therefore, that the present study included only one colored male and three colored females, and that none of the patients worked at heavy labor. Age may be another mitigating factor; the majority of the patients fall into the seventh and eighth decades. Restriction of activity in this period of life probably plays a beneficial rôle in the brighter prognostic picture. The average age of those who died in heart failure was 63.1 years. This suggests that the degenerative processes of old age were in some measure responsible for death. All the patients were followed closely, and congestive failure was treated as soon as detected, with digitalis and mercurial diuretics. With the exception of the six symptomatic patients who died in the first two years of the study, all received the prescribed anti-syphilitic treatment. The exact value of this therapy in prolonging life is also difficult to determine. Padget and Moore<sup>14</sup> report that anti-syphilitic therapy almost doubles the life span in aortic insufficiency. In the New York Hospital Syphilis Clinic, it has been customary to initiate treatment of cardiovascular syphilis with bismuth, and to introduce arsenicals several weeks later. A total of 100 injections of bismuth and 100 injections of arsenic has been arbitrarily chosen, and an effort has been made to continue the therapy without rest periods for four years.

Abnormal widening of the ascending aorta (as shown in table 3) was found in the three groups of patients, in some who died early, and again in some who remained completely asymptomatic throughout the entire period of the study. Although the significance of this finding in prognosis is not clear, it is certainly not always ominous. A low diastolic blood pressure, below 60 mm. of mercury, and, therefore, a low diastolic intra-aortic pressure, was found in only six of the patients in this study, four of whom have died. The significance of this finding, again, is not clear.

Appearance of cardiac decompensation in syphilitic aortic insufficiency is said to be an especially serious sign, as is precordial pain or the finding of an enlarged heart; moreover, digitalis is thought to be less effective than in cardiac disease of other etiology.<sup>3, 5, 15</sup> Nine of the patients were in congestive failure three to nine years previously, were treated with digitalis,



and were alive at the termination of the study. In those who had precordial pain, the survival period was even greater, an average of 9.4 years. It should be emphasized at this point that all but one of the surviving patients were well-compensated and carrying on their respective pursuits, as though they had never had cardiovascular syphilis. Moreover, six of these patients are actually symptomatically improved. Patients with "free" aortic regurgitation have previously been assigned a poor prognosis.<sup>6</sup> But again this was not borne out in the present study, as a "loud" murmur was frequently found in those who had remained asymptomatic throughout, and a "soft" murmur in many who had always been symptomatic.

Of all the tests available, a prolonged circulation time and a low diastolic blood pressure probably offer the best index of prognosis in syphilitic aortic insufficiency.

### SUMMARY

Forty-three patients with syphilitic aortic insufficiency which was intensively treated with bismuth and trivalent arsenicals were followed two to 16 years. In 27 of these individuals, determinations of cardiac efficiency were made in 1941 and again in 1946.

In the five and one-half year period of the investigation, the status of 20 of the 43 patients changed for the worse. In only six of the 18 asymptomatic patients, however, did symptoms develop. Thirteen of the whole group of 43 died, eight of heart disease. Seven had to be reclassified as symptomatic-on-questioning or frankly symptomatic.

At the termination of the study, all the 27 living patients but one were well-compensated despite the duration of their aortic insufficiency (six to 12 years) and were able to continue their usual pursuits. Twelve of the 27 remained completely asymptomatic.

Eleven of the symptomatic patients were maintained on digitalis for two to six years with improvement in compensation. Six of the symptomatic patients actually improved during the period of observation.

### CONCLUSIONS

1. Syphilitic aortic insufficiency may be characterized by an asymptomatic phase of at least two to 10 years.
2. A symptomatic phase usually occurs. This may last two to 14 years.
3. Cardiac failure may be as readily controlled with digitalis and mercurial diuretics as cardiac failure in other types of heart disease.
4. Prolonged circulation time and low diastolic blood pressure offer the best indices for prognosis.

### BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 1944, The Macmillan Company, New York, p. 384.
2. LEVINE, S. A.: Clinical heart disease, 1946, W. B. Saunders Company, Philadelphia, p. 155.

3. MOORE, J. E.: The modern treatment of syphilis, 1944, Charles C. Thomas Company, Baltimore, p. 284.
4. YATER, W. M.: Fundamentals of internal medicine, 1940, Appleton-Century, New York, p. 28.
5. LAMB, A. R., and TURNER, K. B.: Nelson's loose-leaf medicine, 1932, Thomas Nelson and Sons, New York, p. 394A.
6. TICE, FREDERICK: Tice's Practice of medicine, 1944, Prior Company, Hagerstown, Maryland, p. 300.
7. WHITE, P. D.: Cecil's Textbook of medicine, 1943, W. B. Saunders Company, Philadelphia, p. 1092.
8. GRANT, R. T.: After histories for ten years of a thousand men suffering from heart disease. A study in prognosis, *Heart*, 1931-33, xvi, 276.
9. McDERMOTT, W., TOMPSETT, R., and WEBSTER, B.: Syphilitic aortic insufficiency: The asymptomatic phase, *Am. Jr. Med. Sci.*, 1942, cciii, 202.
10. FARR, L., OPPENHEIMER, B. S., and SAGER, R. V.: The circulation time in various clinical conditions using sodium dehydrocholate, *Am. Heart Jr.*, 1933, viii, 766.
11. GOLDBERG, S. J.: The use of calcium gluconate as a circulation time test, *Am. Jr. Med. Sci.*, 1936, cxcii, 36.
12. UNGELEIDER, H. E., and CLARK, C. P.: A study of the transverse diameter of the heart silhouette with prediction table based on the teleroentgenogram, *Am. Heart Jr.*, 1939, xvii, 92.
13. KAMPMEIER, R.: Essentials of syphilology, 1944, J. B. Lippincott Company, Philadelphia, p. 319.
14. PADGET, P., and MOORE, J. E.: The results of treatment in cardiovascular syphilis, *Am. Heart Jr.*, 1935, x, 1017.
15. CHRISTIAN, H. A.: Osler's Principles and practice of medicine, 1944, Appleton-Century, New York, p. 414.

# POST-PARTAL HEART DISEASE\*

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THE subject of heart disease complicated by pregnancy has been one of considerable interest for many years and a voluminous literature has been devoted to its discussion.<sup>1, 2, 3</sup> The reverse of this problem; namely, that of pregnancy complicated by heart disease of the usual etiological types,<sup>4, 5</sup> is an everyday one and certainly deserving of much consideration. However, that the puerperium may sometimes be complicated by a type of heart disease that bears a definite relationship to pregnancy, the puerperal period or both; that possesses a definite clinico-pathological character, and that features a prognosis quite different from the usual types of heart disease is not widely known. This is a separate entity from the so-called "physiologic gestatory heart disease"<sup>6</sup> and the cardiac failure secondary to toxemia of pregnancy<sup>7</sup> or activated glomerular nephritis.<sup>8, 9, 10</sup> "Physiologic gestatory heart disease" is merely the overworked heart of pregnancy, the result of increased cardiac output, increased blood volume,<sup>12</sup> increased velocity of blood flow and diaphragmatic elevation. These factors lead to the development of murmurs, usually systolic in time, changes in cardiac tones, gallop rhythm, pedal edema and roentgenologic evidence of cardiac enlargement. This picture is well known and offers no difficulty as a rule in its correct interpretation. The cardiac failure secondary to toxemia of pregnancy is the response to an acute hypertension according to White<sup>13</sup> and is characterized by its predilection for young primiparas, its occurrence in the last trimester of pregnancy, the associated preëclampsiform or eclamptic symptomatology and its dramatic response to therapeutic abortion. Glomerular nephritis, either the acute phase or the acute exacerbation of the chronic phase, quite commonly makes its appearance during pregnancy and may present mainly as a picture of myocardial failure. The complaints of headache, visual disturbances, weakness, pallor and pedal edema plus the hypertension and the "nephritic urine" aid in its diagnosis.

The type of heart disease to be discussed in this paper, termed by Hull,<sup>14</sup> "post-partal heart disease," is a quite distinct cardiac disease from the above mentioned types.

## HISTORY

Although it is still far from being widely recognized and discussed, post-partum heart disease was undoubtedly referred to by Virchow<sup>15</sup> as long ago

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as 1870 in his discussion of "an idiopathic myocardial degeneration"; according to him, a not infrequent finding in women who died in the puerperium. Porak,<sup>16</sup> in 1880, in addition to corroborating Virchow's work, drew the sage conclusion that "this type of cardiac disease is more morbid than mortal," proving his clinical knowledge of its prognosis by this statement. Blacker,<sup>17</sup> in 1907, and Campbell,<sup>18</sup> in 1923, pointed out the occurrence of a non-valvular type of heart disease both in late pregnancy and the puerperium. Herrmann and King,<sup>19</sup> in 1930, described four cases of myocardial failure appearing during the puerperium which possessed no apparent histories or clinical features referable to the usual etiologic types of heart disease. Williams,<sup>20</sup> in 1933, using a large autopsied series for his information, made the statement that 1.5 per cent of cardiac deaths soon after pregnancy were the result of an idiopathic myocarditis. Since the above reports, more cases have been described and a characteristic clinical syndrome has been developed by Hull and Hafkesbring,<sup>14</sup> Gouley, MacMillan, and Bellet,<sup>21</sup> Musser, Sodeman and Turner,<sup>22</sup> and others.<sup>23, 24</sup>

### CLINICAL FEATURES

The earliest symptoms usually appear from between two to six weeks after parturition. The onset is, as a rule, insidious, early symptoms being pedal edema, dyspnea or cough. This chronicity of onset is merely the rule, as an acute attack of left ventricular failure may herald the appearance of cardiac decompensation. Occasionally, in retrospect, one may connect these symptoms of cardiac failure with vague complaints by the patient of dyspnea, ankle edema and palpitations in the last few weeks of pregnancy which apparently were relieved by delivery. Where the symptoms and signs of pregnancy end and those of post-partal heart disease begin is indeed a difficult clinical decision, but it is known that *true* cardiac failure with its many characteristic signs and symptoms never appears in the condition under discussion until, at earliest, a week or two weeks post-partum. Edema gradually increases in severity, reaching extreme proportions, and effusions in the serous cavities are frequent. As with any myocarditis, there are found cardiac enlargement, usually marked, and a rapid rate, but nearly always regular rhythm. Diastolic gallop rhythm, small volume pulse and anasarca are nearly always to be found. Usually the diastolic blood pressure is elevated and frequently both systolic and diastolic pressures. Laboratory data are non-specific, but quite uniform in some respects. Almost invariably upon fluoroscopic examination of the heart, a grossly dilated heart is seen with no selective enlargement of any particular chamber, only a generalized dilatation. The electrocardiogram is usually abnormal but with no uniform pattern. One point of value in differential diagnosis has suggested itself to the author and is offered purely as a personal observation; namely, that the electrocardiographic changes do not vary from day to day to the extent that one finds in the myocarditis of rheumatic fever, Fiedler's

myocarditis, trichinosis and so forth. The urinalysis varies in no degree from that found in any type of congestive failure and the hemogram and blood chemistry are within normal limits.

One characteristic of post-partal heart disease is the refractoriness to treatment. Compensation is usually much more difficult to attain than in the recognized etiological types of heart disease. Hull has made the observation that morphine and paracenteses afford the greatest relief. This is quite a paradox, considering the promising long term prognosis that these cases usually possess. With the usual cardiac treatment, however, these patients gradually lose their edema and dyspnea. Their gallop rhythm disappears and the blood pressure falls to normal limits. They usually require at least a week and usually much longer, however, to achieve this. In the several series reported from Charity Hospital, it has been noticed that this condition occurs much more frequently in the colored race than in the white race, that it follows the first pregnancy more often than subsequent pregnancies, that the incidence of toxemia of pregnancy and twin births in the patients is higher than usual and that a poor dietary history is often obtained. Embolic phenomena occur with striking frequency.<sup>21, 23</sup> As high as 25 per cent of the patients in Hull and Hidden's<sup>23</sup> series suffered embolic complications. Pulmonary embolism occurs more frequently than peripheral embolism and postmortem examinations have shown the source of these emboli to be from stasis thrombi in the ventricles. An important clinical feature of this type of myocarditis is the good prognosis. Even though recurrences of failure may develop with subsequent pregnancies (Case 1), the large majority of these patients make a complete and final recovery.

#### CASE REPORTS

*Case 1.* E. W., a colored female, age 32 years, was first admitted to Charity Hospital in New Orleans on September 9, 1941, with the chief complaint of shortness of breath and swollen ankles of one week's duration.

**Present Illness:** In 1935, the patient became pregnant, and early in the course of the pregnancy (Case 3 of Gouley, et al.<sup>21</sup>) she began to have headaches, scotomata, dizzy spells, pedal edema and vomiting. These symptoms soon disappeared and there was no interruption of or complication of this pregnancy.

In November of 1940, she again became pregnant, and was delivered by a midwife, uneventfully, in July of 1941. However, during the latter part of this second pregnancy, she again had occasional pedal edema, shortness of breath and a "heavy" sensation in the chest following exertion. During the latter part of August, the patient was awakened at night by a severe pain under the left breast followed soon thereafter by dyspnea, coughing and pedal edema. These symptoms became worse and forced her to come to Charity Hospital.

**Medical History:** No history of rheumatic fever, chorea, diphtheria, scarlet fever or syphilis could be obtained.

**Family History:** The mother died of heart disease but the patient did not know at what age. The cause of the father's death was unknown. There were no other siblings.

**Social History:** The patient's diet consisted mainly of beans and her meals did not include eggs or milk. The patient seldom ate meat, having it only about once a week.

**Physical Examination:** Blood pressure 170 mm. Hg systolic and 128 diastolic. Temperature 99°. Pulse 90. Respirations 60.

**General:** A colored female of about 30 years of age who appeared orthopneic. She was sweating profusely and appeared anxious.

**Head:** Negative. Skull negative. Oral mucosae appeared pale and cyanotic. Fundi appeared normal upon ophthalmoscopic examination. There was no glossitis or cheilosis.

**Neck:** Moderate venous engorgement was present. The thyroid was not palpable.

**Thorax:** Respirations were 60 per minute and labored. On auscultation, crackling râles were heard over both lower lung fields posteriorly and dullness to percussion was found at both lung bases. Breath sounds and voice sounds were diminished.

**Heart:** The apex beat was diffuse. The heart was enlarged to the anterior axillary line in the fifth left interspace. The apical and radial rates were 96 per minute. The rhythm was regular. A protodiastolic sound was demonstrated at the apex. Soft systolic murmurs were heard at the apex and base. These were not transmitted to any great extent.

**Abdomen:** The liver could be palpated seven centimeters below the costal margin. The spleen and kidneys were not palpable.

**Extremities:** Two-plus pitting edema of the lower extremities to the knee level was found.

**Reflexes:** Physiological. No calf pain on pressure.

**Genitalia:** Normal adult female.

**Rectal:** Negative.

The impression on this admission was of hypertensive cardiovascular disease with congestive failure and malnutrition.

**Course:** Morphine, atropine and nasal oxygen were immediately administered to the patient and rapid digitalization was instituted. Diuretics were also given. A venesection was performed and 375 c.c. of blood were removed. The patient showed marked improvement following the phlebotomy, with decreased dyspnea and some alleviation of her other symptoms.

A roentgenogram of the chest, taken on the same day (September 9, 1941), showed cardiac enlargement and congestion of the bases. There was prominence of the lung markings. A blood count on the day of admission showed 4,200,000 red blood cells, hemoglobin 80 per cent. Upon urine analysis, the urine was found to be yellow with an acid reaction. The specific gravity was 1.030. There was a two-plus albumin reaction and the test for sugar was negative. On microscopic examination occasional pus cells and red blood cells per high power field were found. Numerous finely granular casts and hyaline casts were seen. The Kline and Kolmer tests were negative and the serum proteins were 6.76 grams per cent. An electrocardiogram on September 10, 1941 was interpreted as follows: "PR .13. QRS .08. Auricular rate 133. Ventricular rate 133. QRS of low amplitude. T<sub>1</sub> and T<sub>4</sub> inverted. R<sub>1</sub> slurred, S<sub>3</sub> notched. Definite evidence of myocardial disease."

On the third hospital day the patient's condition had markedly improved. The râles and edema had subsided to a great extent and there was only slight dyspnea. The blood pressure in the right arm was 190 mm. Hg systolic and 120 diastolic. The patient's blood pressure on September 15, three days later, was 130 systolic and 82 diastolic in the right arm. The following day no residua of the patient's cardiac failure was evident and she was allowed gradually to increase her activities. The digitalis and other medications were discontinued because of the possibility that this

case was one of post-partial heart disease. An electrocardiogram taken on September 18 still showed electrocardiographic evidence of myocardial disease. There was little or no change from the tracing taken on September 10, eight days previously.

The patient's blood pressure in the right arm on September 18 was 130 systolic and 92 diastolic.

Another roentgenogram of the chest made on the eleventh hospital day, September 20, showed slight enlargement of the cardiac shadow. The congestion in the bases seen in the film made on the day of admission had cleared completely.

The patient's blood pressure, when taken on September 21, was 110 systolic and 80 diastolic. A urinalysis performed on the same day revealed the color to be yellow, the reaction acid, and the specific gravity to be 1.020. There was a two-plus albumin reaction with a negative sugar reaction. On microscopic study, occasional granular casts were found to be present. The urea clearance was reported as 85 per cent the first hour and 80 per cent the second hour.

The report of a blood study done on September 23 showed 65 per cent hemoglobin and a red blood cell count of 3,900,000 per cubic millimeter. The total white and differential white counts were within normal limits. The patient's blood pressure on September 24 was the same as on September 21; namely, 110 systolic and 80 diastolic. The patient was considered at this time to be completely compensated and discharge was contemplated. Four days later, just prior to discharge, the patient was found to have pulsus alternans and, upon discovery of this condition, digitalization and complete bed rest were ordered.

An electrocardiogram on September 29 was reported as follows: "Auricular rate 121. Ventricular 121. PR .12. QRS .085. Sinus tachycardia with left axis deviation.  $T_1$ ,  $T_2$ , and  $T_4$  inverted. Definite electrocardiographic evidence of myocardial disease. The changes from the electrocardiogram made on September 18 may have been due to digitalis. A sound record on September 29 showed a soft systolic and possibly a presystolic murmur at the apex with a soft systolic murmur at the base."

On the following day, September 30, a roentgenogram of the chest showed slight enlargement of the cardiac shadow. The lung fields were clear.

The patient's blood pressure recorded on October 2 was 132 systolic and 106 diastolic. The pulse rate was 90 per minute and pulsus alternans and protodiastolic gallop rhythm were present. On October 9, a roentgenogram of the chest revealed slight enlargement of the cardiac shadow, especially in the region of the left ventricle. The lung fields were clear. The gallop rhythm and pulsus alternans had disappeared during this week. On October 17 physical examination revealed no evidence of congestive failure and two days later she was discharged to the Special Medicine Clinic. The following information was recorded in this Clinic:

On November 8, 1941, there were negative findings on physical examination. Digitalis was discontinued at this time. The patient was next seen on December 6, at which time there were still no abnormal findings.

The patient did not return to the Clinic until January 17, 1942, when she reported that she had a persistent cough. This was apparently the result of an upper respiratory infection. The blood pressure was 130 systolic and 92 diastolic. Codeine and elixir of terpene hydrate were prescribed for her.

The physical findings were still normal on March 28, 1942, her next visit. The patient came to the Clinic on July 11 and complained of dyspnea, substernal pain, vertigo, and nervousness. At this time, again, the physical examination seemed to be without significance. An electrocardiogram on this day was interpreted as, "definite evidence of myocardial disease with no significant change from previous electrocardiograms." On September 15, 1942, when the patient came to the Clinic, she had suffered for three weeks from shortness of breath, paroxysmal nocturnal dyspnea and pedal edema. Upon physical examination, cardiac enlargement was present with

ectopic beats and a soft systolic murmur at the apex. On fluoroscopy, marked left ventricular enlargement was demonstrated. She was immediately digitalized and given instructions regarding restriction of salt and fluids. On October 6, the patient came in with a chief complaint of dizzy spells every two to three hours when she was up and about. Cardiac enlargement was again noted on physical examination. There was a diffuse apex beat and a systolic murmur at the apex and base. The blood pressure was 120 systolic and 60 diastolic, with pulsus alternans, so the patient was admitted for observation.

*Second Admission:* The patient's chief complaints on her second admission were shortness of breath and edema of the ankles of two weeks' duration. Again the patient was placed on a cardiac regime. Following this she achieved a slow but uneventful recovery. The patient was then, again, discharged to the Special Medicine Clinic. She was later admitted to the hospital on March 27, 1945 for gynecological surgery. She withstood this uneventfully and was last seen in July, 1945, in the Special Medicine Clinic, at which time she presented no signs or symptoms of heart disease. In reply to a postcard sent to her in August of 1945, she stated "that she was in good health and was taking no medicine."

*Case 2.* L. M., a 31 year old colored female, was admitted to the Surgery Service on November 17, 1941, with a diagnosis of incarcerated para-umbilical hernia. In the history, it was brought out that following the birth of her first child in December, 1940, she suffered from progressive cardiac failure. Pedal edema, dyspnea and orthopnea were noticed during the last month of pregnancy and, following delivery, they became more pronounced. This condition progressed until she consulted her local physician. Under his treatment, she rapidly became symptom-free and remained so up until the time of this admission, except for slight dyspnea and occasional pedal edema. She was taking no digitalis at the time of admission.

*Past History:* The patient reported no history of rheumatic fever, "inflammatory rheumatism," repeated sore throats or syphilis. There was no history of pyelitis or Bright's disease. Symptoms of pellagra, beri-beri and other nutritional deficiency states were denied.

*Family History:* This was of no significance.

*Social History:* The patient is a housewife who gave a good dietary history. She does not use alcohol or habit-forming drugs, and she lives in clean surroundings.

*Physical Examination:* Blood pressure 134 systolic and 118 diastolic. Pulse rate 125. Respirations 28. Temperature 98.4°.

*General:* The patient was a well developed, well nourished colored female, appearing mildly dyspneic and somewhat apprehensive. The complexion was sallow.

*Head:* There was slight edema of the eyelids. The conjunctivae were pale. Fundi were normal in appearance.

*Neck:* Slightly engorged and pulsating neck veins were noted. The thyroid was not palpable.

*Thorax:* Fine, moist, inspiratory râles were heard at both bases posteriorly.

*Heart:* The point of maximal impulse was in the anterior axillary line in the sixth left intercostal space. The apex beat was forceful and diffuse. Enlargement to the right and left was found upon percussion. A blowing systolic murmur, loudest at the apex and transmitted to the left axillary region, was demonstrated. A diastolic gallop rhythm was present. The apex and radial rates were both 120 per minute and regular.

*Abdomen:* There was evident distention of the abdomen. Questionable shifting dullness and fluid wave were elicited. A para-umbilical hernia, four centimeters in diameter and easily reducible, was present. Liver dullness to three centimeters below the right costal margin was found. There was slight sacral edema.

*Extremities:* There was a two-plus pitting edema of the lower extremities to the knees.



Genitalia: Normal female multipara.

Rectal: Negative.

Neurological: The reflexes were physiologic and there were no abnormal ones present.

*Course:* On November 18, one day following admission, the patient was seized with a sudden attack of dyspnea and severe pain in the left chest. On physical examination, signs of left ventricular failure were found and the patient was immediately administered morphine, atropine, oxygen and intravenous digitalis. She was then transferred to a medical ward where complete cardiac care was instituted.

At that time a hemogram revealed 4,500,000 red blood cells with 90 per cent hemoglobin. There was a white blood cell count of 4,600 with a normal differential. On this same day a urinalysis was performed. The urine was brown in color and there was an acid reaction. The specific gravity was 1.030. There was a four-plus albumin reaction and a negative test for sugar. The sediment showed six to eight white blood cells and two to three red blood cells per high power field. Occasional hyaline casts were seen.

Blood chemistry, also done at this time, demonstrated the following: Urea nitrogen 18.2 mg. per cent, glucose 105 mg. per cent, Kline and Kolmer negative. An electrocardiogram, interpreted by Dr. James L. Gouaux, was reported as: "Auricular rate 110 per minute. Ventricular rate 110 per minute. PR interval 0.15 second, QRS interval 0.08 second. Sinus tachycardia, QRS complexes of low amplitude, all T waves low, T<sub>4</sub> notched. Strongly suggestive of myocardial disease."

A roentgenogram of the chest revealed cardiac enlargement and pulmonary congestion. Fluoroscopy of the chest revealed marked cardiac enlargement, involving all of the chambers. Pulsations were markedly diminished.

The patient responded gradually to her cardiac management with a slow disappearance of the edema, ascites, dyspnea and pulmonary engorgement. Her urine findings reverted to normal and a urea clearance test done on November 30, revealed 100 per cent clearance. An eye ground examination again revealed normal fundi. Her blood pressure was found to be 126 systolic and 86 diastolic on December 18, and 120 systolic and 70 diastolic on December 19. Cardiac fluoroscopy on December 19 revealed no evidence of the previous enlargement. A low grade fever developed on December 20, but, due to the fact that the patient left the hospital against orders, her course could not be followed for evaluation.

In answer to a postcard sent to the patient, she stated that she was "taking no medicine and feeling fine," except for slight occasional symptoms resulting from the hernia.

*Case 3.* D. R., a 21 year old colored female, entered Charity Hospital on March 28, 1944, with the chief complaint of "bad heart and bad kidneys."

*Present Illness:* This dated back to January 21, 1944, when the patient delivered, spontaneously, a seventh month, premature infant, which died soon after birth. During the last month of this pregnancy, which was her first, she had noticed ankle edema, blurred vision and dizziness. She was also told that she had "high blood pressure" at this time. These signs and symptoms disappeared after delivery, but two or three weeks following delivery, she was again troubled with ankle edema. About this same time, she suffered from a "pneumonia," characterized by sudden onset of chest pain, grossly bloody sputum, severe dyspnea and a rapid (four-day) response to sulfadiazine. The ankle edema persisted, however, and gradually dyspnea progressing to orthopnea developed.

*Past History:* No history of lues, rheumatic fever, scarlet fever, diphtheria, pyelitis or nephritis could be obtained. Symptom complexes resembling trichinosis were denied and there was no hypertensive history except during the period prior to delivery.

Review of Systems: Essentially as stated above.

Social History: A fairly good dietary history was obtained, with no particular deficiency in meat, eggs and milk.

Physical Examination: Temperature 99°. Respirations 30. Pulse rate 120. Blood pressure 115 systolic and 95 diastolic.

General: A well developed, well nourished, colored female of about the stated age, who was in severe respiratory difficulty and presented generalized anasarca.

Head: Negative. Eye grounds were normal. No glossitis or cheilosis present.

Neck: The thyroid was not palpable. Venous engorgement was evident and quite severe.

Chest: The chest was symmetrical with no tendency to lag on either side. Dullness to percussion, impaired tactile fremitus and absent breath sounds were demonstrated over the bases of both lungs posteriorly. The point of maximal impulse was in the sixth left intercostal space in the anterior axillary line and quite diffuse in nature. The left border was percussed 12.5 centimeters from the midsternal line. Upon auscultation, a loud protodiastolic gallop sound was heard at the apex. A blowing systolic murmur, not widely transmitted, was also heard at the apex.

Abdomen: The abdomen was visibly distended and both shifting dullness and a fluid wave were demonstrated. The liver was palpated three centimeters below the right costal margin. The spleen and kidneys were not palpable. Sacral edema was present.

Extremities: Three-plus pitting edema of both legs into the thighs. Venous pressure performed in the antecubital fossa area was 230 millimeters of water.

Neurological: Normal reflexes present.

The laboratory work was as follows: The urine was acid in reaction, concentrated to 1.024, and gave a negative reaction for sugar. There was one-plus albumin. The sediment examination was quite normal. The blood picture revealed a mild hypochromic, microcytic anemia with a normal total white and differential white count. The carbon dioxide combining power was 40 volumes per cent; the blood urea nitrogen was 11.1 mg. per cent, and the cholesterol was 180 mg. per cent. The Kline and Kolmer tests were negative.

A roentgenogram of the chest showed marked enlargement of the cardiac shadow to the left and right, with fluid at both bases and passive congestion. The electrocardiogram was read as follows: "Auricular rate 98 per minute. Ventricular rate 98 per minute. PR .16 second. QRS .08 second. T-waves of low amplitude in all leads. Suggestive evidence of myocardial disease."

*Course:* The patient was immediately placed upon a full cardiac regime including digitalis, salt restriction and diuretics and, in addition, was given large doses of the vitamin B complex, both orally and parenterally. Blood cultures were taken on five occasions because of a low grade fever, but all were reported as showing no growth. Repeated urines revealed no significant changes. Repeated electrocardiogram showed no changes from the previously reported one. A slow but gradual response to medication began at the end of the first week in the ward, but thoracentesis was finally resorted to in order to remove the bilateral pleural effusions. Ankle edema, râles, dyspnea and ascites gradually disappeared during the second week. The blood pressure was recorded on April 4, April 5, and April 10, 1944, and upon these three occasions it was found to be 120 systolic and 75 diastolic. The gallop rhythm persisted into the third week before disappearing. Thirty-five pounds of weight were lost in these three weeks. The patient was discharged on April 16, 1944, and followed in the Medicine Clinic, where, on June 22, 1944, digitalis was withdrawn. Up to the present time (October 16, 1945) she writes that she has had no more difficulty.

*Case 4.* E. M. N., a colored female, 21 years of age, was admitted on May 29, 1944, with the complaints of abdominal swelling, swollen ankles and shortness of breath.

**Present Illness:** The patient was delivered of her first child in March, 1944, following an uneventful pregnancy. About two weeks previous to admission, she noticed the appearance of swollen ankles, which gradually became worse. At about this same time, she was aware of a gain in weight and dyspnea upon exertion. This progressed to dyspnea at rest and abdominal distention was first perceived at about this time. She consulted her local physician, but failed to gain any relief. Orthopnea prevented her from restful sleep and one episode of nocturnal dyspnea at this time compelled her entrance into Charity Hospital.

**Review of Symptoms:** Essentially negative except as listed above.

**Past History:** The patient denied by name or symptomatology, rheumatic fever, chorea, syphilis, kidney disease, hypertension, or recent infection of any type.

**Social History:** The patient's diet was quite adequate with no shortages of milk, meat or eggs.

**Physical Examination:** Blood pressure 160 systolic and 110 diastolic. Pulse rate 160 per minute. Respirations 24 per minute. Temperature 98.8° (oral).

**General:** A well-developed, well nourished, colored female of about 20 years of age who was moderately dyspneic and presented evident abdominal enlargement.

**Head:** Negative. Skull negative. Sclerae clear, no exophthalmos. Fundusoscopic examination was negative except for questionable arteriolar spasm. Hearing range and otoscopic examination were negative. Oral mucosa slightly pale. Severe dental caries were present. There were no oral or labial lesions suggesting vitamin deficiency and no glossitis present.

**Neck:** Thyroid was not palpable. Evident venous engorgement was present.

**Thorax:** Fine, moist râles were heard at both lung bases posteriorly.

**Heart:** The heart was enlarged to percussion, the point of maximum impulse being in the left anterior axillary line in the sixth interspace. Apical and radial rates were 100 per minute and quite regular. A Grade II systolic murmur and a diastolic gallop sound were present at the apex.

**Abdomen:** There was marked distention of the abdomen and a fluid wave was elicited. The liver was quite difficult to palpate, but it was thought to be three or four centimeters below the right costal margin.

**Extremities:** Four-plus pitting edema of the legs to the knees was present. The reflexes were normal and there was no hypesthesia or calf tenderness elicited.

**Neurological:** Normal reflexes and no pathologic reflexes present. Pelvic and rectal examinations were negative.

**Course:** The patient was immediately placed upon a cardiac regimen, i.e., rapid digitalization, ammonium chloride, low salt diet and Mercupurin, etc. A roentgenogram the day of admission revealed marked enlargement of the cardiac shadow and passive congestion. Blood chemistry, serology, urinalysis and complete blood study were within normal limits. The electrocardiogram on May 29, revealed the following: "PR 0.16. QRS .08. Auricular and ventricular rate 104 per minute. QT interval definitely prolonged, T<sub>4</sub> inverted. The circulation time (Decholin) from arm to tongue was 19 seconds and the venous pressure was 190 millimeters of water."

The patient showed a poor response to therapy but slowly regained compensation with the aid of two abdominal paracenteses and large amounts of ammonium chloride and Mercupurin. The blood pressure on June 1 was 150 systolic and 100 diastolic, on June 4, 135 systolic and 85 diastolic, on June 11, 120 systolic and 80 diastolic. A second roentgenogram of the chest on June 14 was reported as showing slight increase in lung markings, but otherwise normal. Venous pressure and circulation time were normal on this date and, clinically, the patient was compensated. An electrocardiogram on June 16 was unchanged from the previous one on May 29. Digitalis was discontinued at this time and on June 18 the patient was discharged to Medicine Clinic for weekly follow-ups. Up to the present date (September, 1945) she has progressed uneventfully, without digitalis, diuretics or salt restriction.

*Pathology:* The characteristic gross and microscopic pathology in this unusual type of heart disease is not clearly delineated or defined as yet in the minds of some pathologists. However, it features enough consistent changes to be regarded as quite distinct. Upon gross examination, the heart shows generalized dilatation with only slight hypertrophy evident. The epicardium is usually smooth and glistening and the muscle pale, grayish-brown in color, soft and mottled by congestion. Antemortem thrombi are frequently found enmeshed in the *trabeculae carneae*. The coronary arteries are patulous throughout with smooth intimal surfaces.

Microscopically, the pathology is characterized by focal lesions, only occasionally coalescing to become conglomerate and diffuse. These focal lesions present marked parenchymatous degeneration with irregularly sacculated muscle fibers, "wavy" in appearance because of cytoplasmic loss. Necrotic foci are numerous with varying degrees of cellular infiltration, chiefly lymphocytic, but with occasional neutrophils or eosinophils. A much larger cell with cuboid or oblong nuclei is usually present. These are thought to be the residual nuclei of the degenerated muscle, surrounded by necrotic sarcoplasm. Occasionally, these nuclei may be seen in compact, parallel rows. Hemorrhage into the necrotic areas is frequent. There is no hydropic degeneration of the muscle fibers, eosinophilic infiltration or interstitial edema. Occasionally one sees areas in which the focal lesions have been invaded by fibroblasts and pseudo-giant cells, with replacement of the myocardial nuclei, only acellular scars remaining.

#### PATHOGENESIS

The relationship of pregnancy and the puerperium to this type of heart disease at once raises some interesting questions. Is this condition an atypical hypertensive state stemming from an activated glomerulo-nephritis? The blood pressure readings in the large majority of these patients reveal a mild hypertension. Heart weights at necropsy usually show a moderate increase over normal. Whether this increase in heart weight was due to hypertrophy alone and not to the associated degenerative and edematous character of the pathology is an undecided point. Pathological examination of the kidneys may at times reveal moderate arteriolar sclerosis, areas of septic infarction or simply a congestive nephritis, but the typical features of a glomerulo-nephritis are absent. Pertinent histories, typical urinalyses and compatible clinical features of glomerulo-nephritis have been conspicuous by their absence. True, in some of the cases reported by Sodeman,<sup>6</sup> a clinical picture and urinalysis compatible with that of acute hemorrhagic glomerulo-nephritis was reported, but he divides these postpartal syndromes into a nephritic and a non-nephritic one, confirmed by Addis counts. Musser, Sodeman and Turner,<sup>22</sup> in an earlier article, also divided these two puerperal complications into these same two groups. In their cases, the nephritic

group was without evidence of disease until the puerperal period and developed within a week postpartum signs of sepsis followed in two to three weeks by typical acute hemorrhagic glomerulo-nephritis. They consider this sepsis as a streptococcal puerperal infection with the development of a sensitized state, and the subsequent nephritis following the two to three weeks latent period, the same mechanism as postulated for all acute hemorrhagic glomerulo-nephritis. Their non-nephritic cases showed little evidence of heart disease during pregnancy but developed typical congestive failure two to three weeks post-partum. It is true, however, that the heart failure of acute nephritis at times may show few or no urinary abnormalities<sup>18</sup> but usually hematuria is quite constant.<sup>3</sup> Acute glomerulo-nephritis can be ruled out on the above features in the large majority of cases.

As mentioned in the introduction of this article, toxemia of pregnancy may be complicated by myocardial failure,<sup>13</sup> again, as in glomerulo-nephritis, the result of an acute hypertension. Toxemia of pregnancy bears some resemblance to post-partial myocarditis in that both occur most frequently in young primiparas, especially the negro primipara, and in multiple pregnancies. The fact that toxemia of pregnancy never occurs later than approximately one week post-partially immediately militates against the direct relationship of these two conditions.

Is this condition merely the myocardial failure of an essential hypertensive state? Admittedly, the positive differentiation from post-partum heart disease is extremely difficult, sometimes impossible. Both conditions feature diastolic hypertension and it is obviously impossible in some cases to determine the duration of this hypertension. The absence of a history of hypertension or of hypertensive heart disease prior to pregnancy, absence of signs of left ventricular hypertrophy in the electrocardiogram, the return of cardiac size and the blood pressure to normal limits, and the younger age group would all tend to cast considerable doubt as to the identity of this condition with essential hypertensive heart disease. Funduscopic examinations in these reported cases revealed signs of a chronic hypertension and the kidney function was well within normal limits, considering the congestive state. Renal arteriosclerosis is usually absent at autopsy<sup>21</sup> and when present is of a mild nature, indicating a hypertension of short duration. Moreover, the reported histopathology of the cardiac muscle is certainly not that of chronic hypertension.

Hull<sup>14</sup> makes the statement that the clinical pictures of cardiac beri-beri and post-partial heart disease are identical if one disregards the neurological features of beri-beri heart disease. White,<sup>13, 25</sup> however, indicates that in beri-beri heart disease the neurological phenomena are occasionally absent, the avitaminosis being manifested entirely as pure cardiac failure. Undoubtedly, some of the cases reported by Hull<sup>14</sup> and Gouley et al.<sup>21</sup> and one of the cases reported in this paper had a grossly deficient diet during pregnancy. Thus, it would seem as though post-partial heart disease could at

least be a conditioned variant of beri-beri heart disease. If so, why the refractoriness to specific vitamin therapy and why its occurrence post-partum when vitamin requirements would certainly tend to be lowered? Again, why the difference in pathology in the two conditions? True, fragmentation of the muscle fibers is common to both conditions, but the hyaline and fatty degeneration found in beri-beri heart<sup>25</sup> has not been reported in post-partal heart disease. Until these questions are answered, these two conditions must be considered as distinct clinico-pathological entities.

It is recognized that rheumatic heart disease may present in varied clinical pictures, but the absence of a rheumatic history, the distinct differences in the clinical course, the absence of typical murmurs and, above all, the different pathological features would tend to rule out such a diagnosis.

The possibility that post-partum heart disease might be related to an infectious process was first entertained by Virchow.<sup>15</sup> Gouley et al.<sup>21</sup> have discussed the causal influences of infection only to reject them. With the exception of one case, none of their patients presented any evidences of infection and necropsy only verified this clinical opinion. This one case died with a *Staphylococcus aureus* septicemia resulting from a stubborn bed sore, the result of three months of cardiac decompensation and obviously not its cause.

The clinical picture and also the gross appearance at autopsy resembled that rare form of myocarditis, usually given the name, "Fiedler's myocarditis."<sup>20, 27</sup> Most authorities consider this to possess an infectious etiology, but, in view of the varied precipitating and accompanying conditions associated with it, this opinion must be treated with considerable doubt. The pathology of this disease is usually reported as chiefly interstitial, but some cases revealed an associated parenchymal involvement with dissolution of the myocardial substance and the appearance of "myogenous" cells.<sup>21</sup> Saphir<sup>26</sup> has stated that two distinct types of myocarditis have been described pathologically for Fiedler's myocarditis, one a granulomatous and the other a diffuse inflammatory process. Obviously, in the light of such a vague pathological state, post-partum myocarditis could easily be mistaken by the pathologist for Fiedler's myocarditis. However, as far as can be ascertained, no reference has ever been made to pregnancy or the puerperium as having any bearing on the clinical course or possible etiologic relationship to Fiedler's myocarditis. It is worth reminder, however, that in view of the varied precipitating causes of Fiedler's myocarditis, pregnancy and the puerperium could act in a similar manner. Indeed, the exact clinical and pathological picture of post-partal heart disease has been reported in males<sup>28</sup> following upper respiratory infections. Eventually, as familiarity with the clinico-pathological picture is gained, all of these vague forms of myocarditis may be recognized as equivalents varying only in their predisposing and precipitating factors and possessing one of several types of recognized pathology.

## TREATMENT

Although there is usually a response to the measures used commonly in the treatment of heart failure, it is not a striking one. Recovery is measured in terms of weeks and, in some cases, months, differing somewhat from the cardiac failure due to the usual etiological types of heart disease. It is hardly justifiable, nevertheless, to omit any detail of a vigorous therapeutic regime. Digitalis should be used to the full limit of efficiency and should be supplemented by the mercurial diuretics, and by salt and water restriction. Mechanical removal of fluid collections is usually more efficacious than the mercurial diuretics, since, for some reason, these patients respond poorly to the latter. Oxygen and Demerol injections are indicated during the acute attacks of dyspnea, so frequent in this condition. Measures directed against any possible pathogenetic factors are justified and a diet high in vitamins and proteins supplemented with iron is a standardized procedure. Because of the possible relationship of post-partal heart disease to the sudden increase in activity following delivery,<sup>6</sup> rest in bed should continue for several weeks after all edema has subsided and resumption of normal activity should be gradual. The immediate outlook for these patients is good, as the large majority make a slow but uneventful recovery, but this condition may recur following subsequent pregnancies and the patient should be informed of this fact. Two such episodes of failure should certainly justify sterilization.

## BIBLIOGRAPHY

1. BREED, W. B., and WHITE, P. D.: Heart disease in pregnancy, Boston Med. and Surg. Jr., 1923, clxxxviii, 984.
2. HAMILTON, B. E., and KELLOGG, F. S.: Cardiac disease in pregnancy, Jr. Am. Med. Assoc., 1928, xci, 1942.
3. MACKENZIE, J.: Heart disease and pregnancy, Oxford Medical Publications, Henry Frowde; Hodder and Stoughton, London, 1921.
4. DONOVAN, H. C.: Heart disease complicating pregnancy, Brit. Med. Jr., 1927, xiv, 83.
5. STANDER, H. J., and KUDER, K.: The treatment of heart disease complicating pregnancy, Jr. Am. Med. Assoc., 1937, cviii, 2092.
6. SODEMAN, W. A.: Cardiac changes in pregnancy unrelated to the usual etiological types of heart disease, Am. Heart Jr., 1940, xix, 385-397.
7. FISHBERG, A. M.: Hypertension and nephritis, 4th Edition, Lea and Febiger, Philadelphia, p. 755.
8. MASTER, A. M., JAFFE, H. L., and DACK, S.: The heart in acute nephritis, Arch. Int. Med., 1937, lx, 1012-1016.
9. FELLER, A. E., and HUREVITZ, H. M.: Acute nephritis with cardiac failure, Am. Heart Jr., 1938, xvi, 568.
10. WHITEHILL, M. R., LONGCOPE, W. T., and WILLIAMS, R.: The occurrence and significance of myocardial failure in acute hemorrhagic nephritis, Bull. Johns Hopkins Hosp., 1939, lxiv, 83.
11. BURWELL, C. S., and STRAYHORN, W. D.: Observations on the circulation during and after pregnancy, Jr. Clin. Invest., 1933, xii, 977.
12. BURWELL, C. S., STRAYHORN, W. D., FLICKINGER, D., CORLETTE, M. B., BOWERMAN, E. P., and KENNEDY, J. A.: Circulation during pregnancy, Arch. Int. Med., 1938, lxii, 979.

13. WHITE, PAUL DUDLEY: Heart disease, 3rd Edition, The Macmillan Co., New York, p. 558.
14. HULL, EDGAR, and HAFKESBRING, E.: "Toxic" post-partal heart disease, New Orleans Med. and Surg. Jr., 1937, lxxxix, 550-557.
15. VIRCHOW, R.: Sitzung der Berliner Geburtshilflicher Gesellschaft.
16. PORAK, C.: De l'influence réciproque de la grossesse et des maladies du coeur, Thesis, Paris, 1880.
17. BLACKER, G. F.: British Med. Jr., 1907, i, 1225.
18. CAMPBELL, D. G.: Pregnancy and heart disease, Canadian Med. Jr., 1923, xiii, 244.
19. HERRMANN, G. R., and KING, E. L.: Cardiovascular disturbances in the obstetrical patient, Jr. Am. Med. Assoc., 1930, xcv, 1472.
20. WILLIAMS, P. F.: Causes of post-partal deaths, Weekly Roster and Med. Digest, 1933, xxviii, 7.
21. GOULEY, B. A., MACMILLAN, T. M., and BELLET, SAMUEL: Idiopathic myocardial degeneration associated with pregnancy and especially the puerperium, Am. Jr. Med. Sci., 1937, cxciv, 185-199.
22. MUSSER, J. H., SODEMAN, W. A., and TURNER, R. H.: Heart failure or acute nephritis with onset about three weeks after delivery, Ann. Int. Med., 1938, xii, 739-753.
23. HULL, EDGAR, and HIDDEN, ELEANOR: Post-partum heart failure, South. Med. Jr., 1938, xxxi, 265.
24. VILTER, R. W., and MCKEE, E. E.: Post-partum myocardosis, Ohio State Med. Jr., 1943, xxxix, 142-144.
25. WERECKEBACK, K. F.: Heart and circulation in tropical avitaminosis (beri-beri), Lancet, 1928, ii, 265.
26. SAPHIR, O.: Myocarditis, a general review, with an analysis of 240 cases, Arch. Path., 1941, xxxii, 1000.
27. SCOTT, R. W., and SAPHIR, O.: Acute isolated myocarditis, Am. Heart Jr., 1929, v, 129.
28. ROESLER, R. W., and SOLOFF, L. A.: Report of a case of left ventricular failure with unusual anatomical changes in the myocardium, Ann. Int. Med., 1935, ix, 477.



# HEREDITARY POLYCYSTIC KIDNEY \*

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THE condition of polycystic kidney is also known as cystic disease of the kidney, cystic degeneration or congenital polycystic kidneys. The disease has always created interest because of the enormous size these kidneys may attain. It is encountered in infants but appears most often between the fortieth and sixtieth years. This is clearly noted in table 2 of this study. It normally has been found to be more common in the female than the male; however, this study disclosed more males than females (table 1).

TABLE I  
Progeny of Generation II No. 6 (2 Generations)

	Positive Male	Negative Male	Positive Female	Negative Female
Positive male produced	2	3	4	1
Negative male produced	1	2	0	2
Positive female produced	4	3	1	1
Total	7	8	5	4
Total—Positive 12 and Negative 12				

TABLE II  
Summary of Dead Positive Members in Generations II, III, IV

	20-30	30-40	40-50	50-60
Positive males	—	—	2	6
Positive females	1	—	2	2

## ETIOLOGY

Several theories have been presented but this paper will deal only with the hereditary factor. The coöperation of the family was unsatisfactory in many instances; however, enough data were acquired to form a basis for determining the hereditary trait.

*Hereditary Factor.* A marked hereditary tendency has always been noted in polycystic kidneys. In this study of the hereditary trait only those members are considered positive about whom enough clinical data were acquired to justify the diagnosis. All other members have been considered negative. The progeny of Generation II No. 6 for two generations is considered as the basis for determining the hereditary trait because these individuals are advanced in years and a fairly definite evaluation of each case

\* Received for publication May 20, 1946.

can be made. The summary of this group (table 1) shows a 1:1 ratio of males produced by positive parents. It also shows a 1:1 ratio of females produced by positive parents. Positive males produce positive and negative males and females. Positive females produce positive and negative males and females. Generation III No. 4 is considered negative and is known to have produced one positive son. The other members of this family are considered negative because the history is inadequate. The patient died at the age of 67 of a cerebral vascular accident, which is a common terminal event in case of polycystic kidneys. His advanced age, however, is against his having polycystic kidneys, although some have been known to reach 80 years of age.

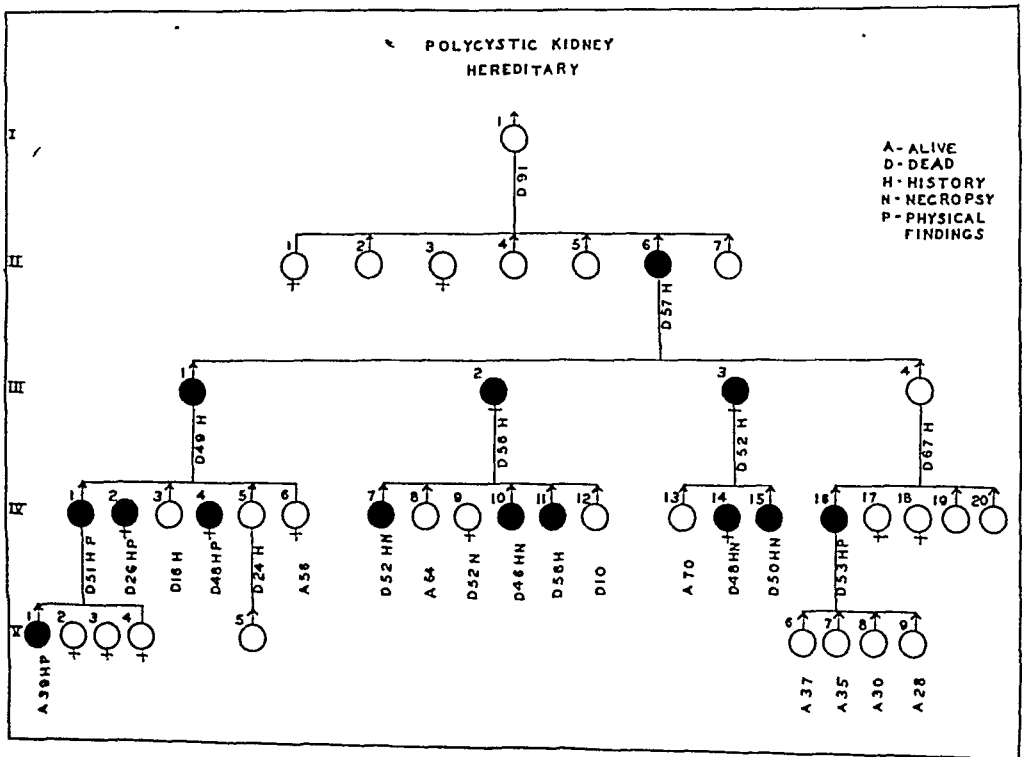


FIG. 1.

This summary shows a total of 12 positive and 12 negative members in two generations. It is concluded the trait is carried as a dominant factor and is not sex-linked.

*Morbid Anatomy.* Although unilateral polycystic kidneys have been noted, the examples presented in this study are bilateral. Figure 2 is a roentgenogram taken of a kidney removed at postmortem examination. The size, as indicated in inches, shows the organ a great deal larger than normal but the configuration of the kidney remains. The cysts have practically replaced the whole kidney. On gross examination no normal kidney parenchyma could be seen. Several autopsies were done and not reported in this case study.

*Symptoms.* The most important and first symptom is that of pain. The degree of pain varies from a heavy sensation at the onset to more severe pain as the kidney becomes larger. Hematuria is a very common finding in this group. It is known to occur during the second decade and to be one of the first symptoms. It is intermittent and profuse but caused no fatalities in this group. A palpable mass with progressive enlargement has been noted. This, however, was not as important a symptom as the pain and hematuria. Signs of chronic nephritis with albuminuria and hypertension were common.

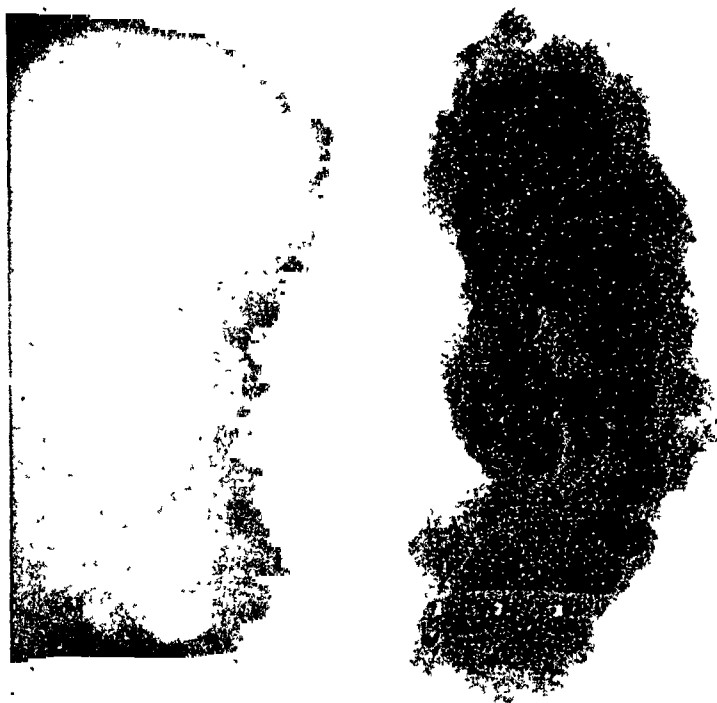


FIG. 2. Roentgenogram of a polycystic kidney removed at autopsy.

*Life Expectancy.* A summary of the members of the family who have died is given in table 2. This summary shows that only one member of 13 died in the 40 to 60 age group. The average life span of all members in the above generations is above 47 years.

*Treatment.* There have been no operative procedures carried out on any members of this group. Treatment was chiefly palliative as symptoms appeared.

#### CASE REPORTS

*Case 1, Generation II, No. 6,* a white male born in 1831 and died in 1888 at 57 years of age. The patient came to America from England in about 1850. He had

the usual history of intermittent hematuria. It is well recognized by the family that this patient died of polycystic kidney.

*Case 2*, Generation III, No. 1, a white male born in 1854 and died in 1903 at 49 years of age. He died of polycystic kidney, having had intermittent hematuria and the symptoms known by the family to be associated with the disease.

*Case 3*, Generation III, No. 2, a white female born in 1855 and died in 1911 at 56 years of age of polycystic kidneys with the usual associated symptoms.

*Case 4*, Generation III, No. 3, a white female born in 1857 and died in 1909 of polycystic kidneys.

*Case 5*, Generation III, No. 4, a white male born in 1859 and died in 1923 at 67 years of age of a cerebral vascular accident. No autopsy was performed. The presence or absence of polycystic kidneys was not definitely known, and this case is considered as negative in figure 1. His one son definitely had and died of polycystic kidneys. This finding would lead one to think the patient had the disease and the presence of polycystic kidneys was probably the cause of hypertension, resulting in a cerebral vascular accident.

*Case 6*, Generation IV, No. 1, a white male, bank cashier, born in 1879 and died in 1930 at the age of 51 years. This patient was first examined two years before his death. The diagnosis at the time of admission was acute vesiculitis, vasitis, epididymitis and polycystic kidneys. His chief complaint was frequency of urination for one month's duration. After a tooth extraction the left testicle became red, swollen and excruciatingly painful. The patient noted gross hematuria and later pyuria. He had lost some weight and had not noted edema or palpitations.

Physical examination revealed a hard, swollen, tender, left testicle. The cord through the entire canal was swollen and tender. The left lobe of the prostate and vesicle were slightly enlarged and very tender. Examination of the abdomen showed a large mass in his left abdomen, reaching almost to the crest of the ilium. Roentgen examination of the abdomen showed an indefinite shadow which corresponded to the palpated mass and also a smaller mass on the right side. Fluoroscopy of the gastrointestinal tract showed the entire stomach to be displaced to the right.

The hemoglobin was 75 per cent, the red blood cell count 3,940,000 and the white blood cell count was 9,500. The blood urea nitrogen was 39.2 mg. per 100 c.c. The urinalysis revealed a specific gravity of 1.010 and was negative for albumin and sugar. Microscopic examination showed numerous white blood cells. The systolic blood pressure at times reached 190 mm. Hg and the diastolic was 90.

A diagnosis of polycystic kidneys, vesiculitis, vasitis, epididymitis and hypertension was made.

*Case 7*, Generation IV, No. 2, a white female born in 1882 and died in 1908. She had a definite history of polycystic kidney with the usual symptoms of hematuria and masses in the abdomen.

*Case 8*, Generation IV, No. 3, a white boy, killed in an accident at 16 years of age. He is considered normal in this study.

*Case 9*, Generation IV, No. 4, a white female, bookkeeper, born in 1887 and died in 1935 at 48 years of age. The patient was examined a few months before her death. She had first noted signs of kidney disease at 40 years of age, at which time she first noted intermittent hematuria which had continued until she was admitted for study. She had also noted palpable abdominal masses. The patient weighed 137 pounds. The skin was pale. The systolic blood pressure was 170 mm. Hg and the diastolic was 95. There were large masses palpable in both sides of the abdomen, the right larger than the left.

The hemoglobin was 48 per cent, the red blood cell count 2,320,000 and the white blood cell count 5,100. The blood urea nitrogen was 76 mg. per 100 c.c. The urine was grossly bloody.

Transfusions were given and the patient survived the episode only to die the same year some time after another hemorrhage.

A diagnosis of polycystic kidneys, hematuria and hypertension was made.

*Case 10*, Generation IV, No. 5, a white male, born in 1888 and died in 1912 at 24 years of age. He had no history of kidney disease. His son and grandson have shown no evidence of kidney disease.

*Case 11*, Generation IV, No. 6, a white female alive at 56 years with no history or physical findings of kidney disease.

*Case 12*, Generation IV, No. 7, a white male farmer born in 1879 and died in 1931 at 52 years of age. The patient had five living, well children. His chief complaints were dizziness, backache and dysuria. The patient had noted increasing symptoms of dizziness and nocturia for three to four weeks. He was aware of large masses in the right and left upper abdomen. He had previously had symptoms of nausea, vomiting, constipation, thirst, vertigo, chills, fever and diplopia. His backache had been present for years. He had marked urgency but could not void. He noted a knife-like pain which radiated from the lower abdomen to the bladder. He had noted no hematuria or discharge.

He was a large, pale, white male, 74 inches tall. His respirations were 20 per minute and the pulse was 84. Examination of the abdomen revealed a large, nodular, firm mass in each upper quadrant. There was a bulging in the left kidney region and tenderness over both kidney areas.

The hemoglobin was 79 per cent, the red blood cell count 4,290,000 and the white blood cell count 10,300. The blood urea was 49 mg. per 100 c.c.

The urine at no time had a specific gravity over 1.010. All examinations revealed a one-plus albumin and were otherwise negative.

The course was steadily downward and the patient died in coma.

The postmortem examination was limited to the abdomen. There was no free fluid in the abdominal cavity. The stomach was markedly dilated and extended below the umbilicus. The spleen was slightly enlarged. The liver and pancreas were normal.

About 6 cm. below the pylorus were two masses of gray, lobulated tissue in and under the serosa of the duodenum. Each mass measured 2.5 by 1 by 0.5 cm.

Microscopic section showed the masses to be made up of pancreatic tissue. One gave evidence of possible early malignant changes.

Both kidneys showed a polycystic involvement. No grossly normal tissue could be demonstrated. The left kidney measured 32 by 15 by 13 cm. and weighed 2,368 grams. The right kidney measured 30 by 17 by 10 cm. and weighed 2,358 grams.

Postmortem diagnosis: (1) Polycystic kidneys. (2) Accessory pancreatic tissue in the wall of the duodenum showing possible early malignancy. (3) Dilatation of the stomach.

*Case 13*, Generation IV, No. 8, a white male born in 1882, at present alive and well, showing no evidence of kidney disease.

*Case 14*, Generation IV, No. 9, a white female born in 1884 and died in 1936 at 52 years of age. The clinical diagnosis was acute pancreatitis and cholecystitis. An operation revealed extensive fat necrosis. An autopsy was performed and was limited to the abdomen. The pathological diagnosis was acute hemorrhagic pancreatitis with necrosis. The kidneys appeared to be normal.

*Case 15*, Generation IV, No. 10, white male, born in 1886 and died in 1932 at 46 years of age.

The patient entered the hospital with a diagnosis of convulsion, chronic interstitial nephritis, chronic myocarditis and arteriosclerosis.

The patient's history revealed a loss of weight during the past year. He had marked peripheral edema. The heart rate had been rapid and the blood pressure elevated.

The hemoglobin was 85 per cent, the red blood cells 4,440,000 and the white blood cell count 18,250 with a normal differential. The blood urea nitrogen was 18.2 mg. per 100 c.c. The urine was grossly bloody.

Diagnosis: Polycystic kidney, hypertension, hematuria. Clinical diagnosis as to cause of death was coronary thrombosis.

The postmortem examination was limited to the abdomen. All the organs appeared normal except the kidneys. Each kidney measured 25 by 15 by 12 cm. and was remarkably involved in a polycystic condition. No uninvolved kidney substance was seen on gross examination.

*Case 16*, Generation IV, No. 11, white male born in 1889 and died in 1939 at 50 years of age. A definite knowledge of polycystic kidney was present.

*Case 17*, Generation IV, No. 12, a white boy born in 1890 and died in 1900 of diphtheria.

*Case 18*, Generation IV, No. 13, a white male born in 1876, alive and well at present. He has shown no signs of polycystic kidneys.

*Case 19*, Generation IV, No. 14, a white female born in 1878 and died in 1926. The patient was first seen when she was 47 years of age, at which time a diagnosis was made of polycystic kidneys, secondary anemia and chronic myocarditis.

Her past history showed a cerebral vascular accident at 41 years of age, affecting the whole left side of the body. She had two living, well children at the time of this examination. She passed uneventfully through the menopause at 45 years of age.

Her chief complaints were swelling of the feet and dyspnea of six weeks' duration. During the past two weeks she had noted orthopnea. She had also noted swelling of the eyelids and a "lemon yellow pallor."

On physical examination she was a chronically ill white female with the important finding of an irregular abdomen. There was a large mass palpable in each upper quadrant extending below the crest of the ilium. The systolic blood pressure was 220 mm. of Hg and the diastolic 110. The hemoglobin was 45 per cent, the red blood count 2,320,000 and the white blood cell count 5,900, with 6 per cent eosinophiles. The 24 hour urine output averaged 1,580 c.c. The specific gravity never exceeded 1.010. There was a faint trace of albumin but otherwise the findings were negative.

The patient became steadily weaker and died at 52 years of age. Autopsy disclosed bilateral polycystic kidneys.

*Case 20*, Generation IV, No. 15, a white male born in 1883 and died in 1933 of polycystic kidneys.

The patient's chief complaints were a darker than usual urine of several days' duration. Urgency and frequency became so severe that he voided every five to ten minutes, at which time he passed small amounts of bloody urine. The urine stream was of normal size but would stop abruptly. After micturition he noted a severe pain radiating to the end of the penis. He had noted no blood clots.

His past history revealed similar symptoms eight years previously and also three months previously.

On physical examination he was markedly emaciated, 76 inches tall. The skin was dry and scaly. Abdominal examination disclosed a mass on each side extending from the kidney area to below the crest of the ilium.

The hemoglobin was 85 per cent, the red blood cell count 4,520,000 and the white blood cell count 8,200. The blood calcium was 10.0 mg. per 100 c.c. The creatinine 6.7. The blood sugar was 140 mg. per 100 c.c. The blood urea nitrogen on admission was 77 and increased to 230 mg. per cent during two months' hospitalization. Urinalysis showed a specific gravity of 1.010 and a one-plus albumin; and microscopically there were numerous red blood cells.

The patient developed a series of convulsions and died after two months' hospitalization.

Postmortem examination was limited to the abdomen. The gall-bladder was

distended to about 6 cm. in width and was 12 cm. in length. No stones were palpable. There was an old healed scar of a duodenal ulcer.

The left kidney extended the entire length of the left abdomen, lifted the diaphragm on that side and extended into the pelvis. It showed numerous cysts, some of which were hemorrhagic. The right kidney was cystic and hemorrhagic, but smaller than the left.

Autopsy diagnosis: (1) Polycystic kidneys. (2) Chronic cholecystitis. (3) Old healed duodenal ulcer. (4) Marked emaciation.

*Case 21*, Generation IV, No. 16, a white male, born in 1884 and died in 1937 at 53 years of age.

The patient was first seen three years before his death. He complained of nocturia, pain in the left side and palpable masses in the kidney areas. His temperature was 103.4° F., the systolic blood pressure was 134 mm. Hg and the diastolic was 74. The patient recovered from the episode.

The second admission was two years later at which time he complained of acute right upper abdominal pain. The patient was noted as being well developed and well nourished. His height was 70 inches and he weighed 185 pounds. There was tenderness and marked rigidity over the upper abdomen. There was a palpable mass in the area of the gall-bladder. There had been no previous attacks of gall-bladder trouble and no jaundice.

The white blood cell count was 38,400. The blood urea nitrogen ranged up to 79.8 mg. per cent. The urine examination showed a specific gravity of 1.011 and was negative for albumin, sugar and red cells.

Record of Operation: There was a mass in the right upper abdomen extending down to the umbilicus. On opening the abdomen a greatly enlarged and thickened gall-bladder was exposed. On excision of the gall-bladder, stones were observed. Stones were impacted in the cystic duct. Two greatly enlarged, polycystic kidneys were observed.

Diagnosis: (1) Acute and chronic cholecystitis with cholelithiasis. (2) Polycystic kidneys.

*Case 22*, Generation IV, Nos. 16, 17, 18, 19, were considered negative because data were inadequate.

*Case 23*, Generation V, No. 1, a white male, grocer, born in 1908. He was first observed in 1927 for a toxic thyroid, which was removed. The patient first noted symptoms referable to the kidneys in 1943. He has noted backache and hematuria, and masses in the abdomen. He has polycystic kidneys.

*Case 24*, Generation V, No. 6, a white male born in 1909. This patient has a dull, heavy sensation over the kidney areas, first noted in 1944. Repeated urinalyses have been negative. Intravenous pyelography has been negative.

This patient is considered negative in spite of suggestive symptoms.

## CONCLUSIONS

1. A large family tree of polycystic kidney is presented.
2. The disease occurred through four generations.
3. The family tree is sufficiently large to serve as a basis for determining the type of hereditary trait.
4. The trait is carried as a dominant characteristic. It is not sex-linked.
5. The incidence is equal in males and females.
6. All but one member died between the ages of 40 and 60 years.
7. The onset of symptoms may be early and consist of backache, intermittent hematuria, palpable masses in the abdomen.
8. The kidneys reach enormous size, some weighing over 2,000 grams.
9. Histories and necropsy findings on several cases are presented.

# CASE REPORTS

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## TOXICITY OF LARGE DOSES OF VITAMIN D (ERTRON) \*

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VITAMIN D has been used for its anti-rachitic properties, uneventfully, for about 20 years. Relatively recently, large doses of vitamin D have been used in the treatment of rheumatoid arthritis. Perhaps the primary reason for this has been the deluge of literature and advertising which has descended upon the medical profession, concerning the efficacy and low toxicity of an activated, heat-vaporized ergosterol made by the Whittier process. Both of these beliefs must be questioned.

### VITAMIN D

The rôle of vitamin D in the prevention and treatment of rickets is well known. The precise mode of action of this vitamin is not completely understood, but it is believed to increase the absorption of calcium and phosphorus from the bowel. Thus administration of vitamin D in rickets will convert a negative calcium balance into a positive one. When given in very high dosage, toxic effects may follow.

### LARGE DOSES OF VITAMIN D IN RHEUMATOID ARTHRITIS

Numerous reports have appeared in the literature concerning this form of therapy. Several authors <sup>1, 2</sup> have reported favorably on the action of large doses of vitamin D (Ertron), mentioning the feeling of well-being of the patient, weight gain, and the return of the hemoglobin and red blood count to normal. Toxicity was minimized. Other observers have reported vitamin D to be of "little or no value in rheumatoid arthritis." <sup>3, 4</sup> Freyberg <sup>5</sup> states that "of the many newer forms of therapy for chronic arthritis, one of the most highly advertised is treatment with massive doses of vitamin D. . . . Benefit attributed to the vitamin occurs relatively seldom and usually is rather slight." Wagner <sup>6</sup> reported good results in six of 42 patients, using 200,000 to 300,000 units daily.

The efficacy of large doses of vitamin D in the treatment of rheumatoid arthritis is apparently unpredictable and very variable, differing greatly in the hands of different observers.

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## TOXICITY OF LARGE DOSES OF VITAMIN D

Numerous articles<sup>3, 4, 5, 7-12</sup> have appeared reporting the toxicity of large doses of irradiated ergosterol and other forms of vitamin D. As early as 1929 an editorial in the *Journal of the American Medical Association*<sup>7</sup> warned that irradiated ergosterol may cause impaired nutrition, weight loss, hypercalcemia, and abnormal calcium deposits in various tissues and organs. Abrams and Bauer<sup>4</sup> reported frequent toxic symptoms following the use of 200,000 USP units vitamin D daily in patients with rheumatoid arthritis. Freyberg<sup>5</sup> stated that in 16 per cent of patients receiving large doses of vitamin D the medication had to be discontinued because of toxicity. Another observer<sup>10</sup> reported that 18 of 31 arthritic patients treated with vitamin D (Ertron) developed toxic manifestations.

The more common symptoms of vitamin D intoxication<sup>13, 14</sup> are nausea, vomiting, anorexia, abdominal pain, diarrhea, weakness, lassitude, headache, pruritus, and polyuria. Renal calcification may inaugurate a train of urinary complaints. Brownish skin pigmentation has been noted.<sup>15</sup>

Metastatic calcification in various tissues and organs and death have been noted in animals<sup>3, 4, 8, 12, 16, 17</sup> and man.<sup>7, 11, 12, 14, 17, 18, 19</sup> Six patients have died and have been autopsied following hypervitaminosis D.<sup>14, 17, 18, 19</sup> Metastatic calcification was noted in all of these patients, and involved chiefly the kidneys, stomach, lungs, and arteries.

## CASE REPORT

E. V. S., 59 year old white male, was first seen on July 11, 1946, when he entered the hospital because of severe arthritic pain of most of the joints of the body, including fingers, wrists, elbows, shoulders, vertebrae, and knees, and because of the appearance of nodules on both arms. The past history revealed that the patient first noted arthritic pains of the neck 22 years ago. The arthritic pains spread slowly to other joints of the body, but did not involve the joints of the hands until 1940. One and one-half years before his present admission the patient developed massive swelling, redness, tenderness, and severe pain involving the joints of the fingers, both hands, and both wrists. There was also an exacerbation of the pain of both elbows, shoulders, and knees. The patient was placed on vitamin D (Ertron) 200,000 units a day, by his physician. This had no effect on his arthritis, but the patient noted anorexia and nausea one month after the onset of Ertron therapy. He had no abdominal pain and no vomiting. Three months after the onset of vitamin D therapy, he was told by his physician that he was anemic, and he received some unknown therapy for this. Six months after the onset of vitamin D treatment, he noted progression of his arthritis, both symptomatically (pain) and objectively (tenderness, limitation of motion, and increasing deformity), the development of nocturia and dysuria, and a 40 pound weight loss. The patient was hospitalized in August 1945, but his hospital physicians at that time apparently did not know that the patient was on vitamin D therapy. Pertinent findings from that hospital admission were as follows: Blood pressure 145 mm. of mercury systolic and 100 mm. diastolic. Examination of the head, eyes, ears, nose and throat were within normal limits. The lungs were clear. Examination of the heart was unremarkable. Examination of the abdomen gave negative findings. The prostate was moderately enlarged and firm. There was no generalized lymphadenopathy. There was limitation of motion of the neck with tenderness over the cervical vertebrae. There was tenderness and swelling of the phalangeal joints of the fingers of both hands. Laboratory work included an electrocardiogram which was normal except for

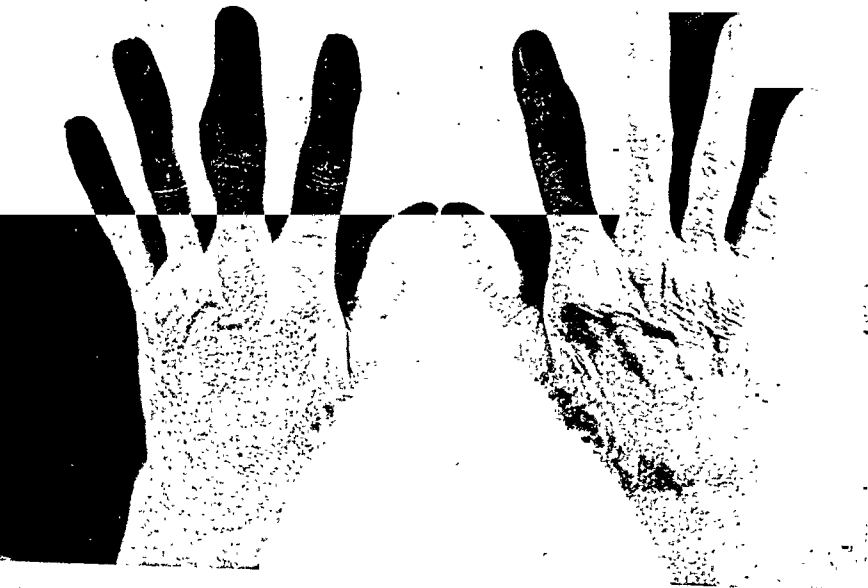
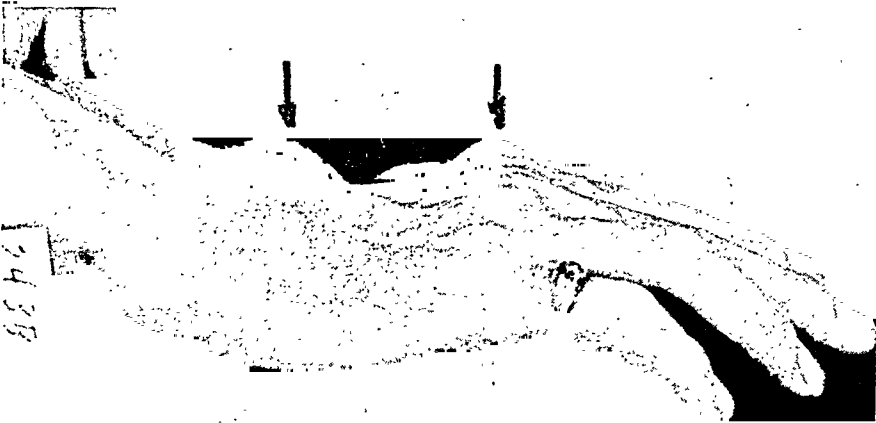
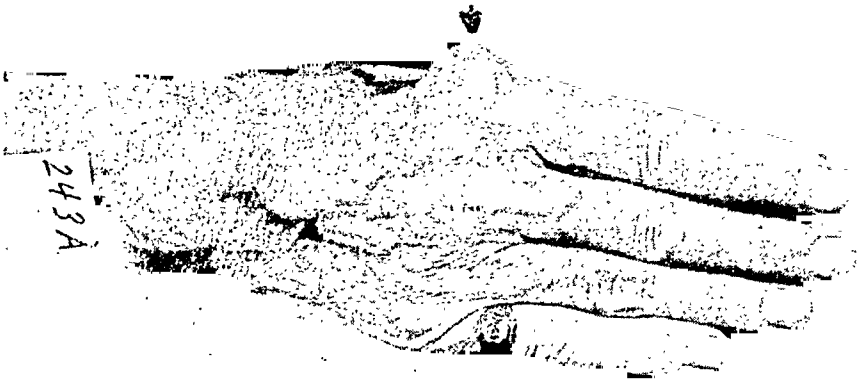


FIG. 1. (Top) Right hand. Note prominence at base of index finger. This was very hard. Atrophy of small hand muscles can be seen.

FIG. 2. (Center) Prominence at base of right index finger and firm swelling ("ganglion") of dorsum of wrist. At operation, the ganglion was found to contain milky fluid and the surrounding soft tissue contained calcium.

FIG. 3. (Bottom) Fusiform left third finger. Compare with figure 4.

left axis deviation; hemoglobin 13.1 gm./100 c.c. blood; red blood cells 4.0 million per cubic mm.; white blood count 6250/cu.mm. with normal differential count; and a negative blood Kahn test. The sedimentation rate was elevated to 48 mm. in 45 minutes (modified Westergren method). Examination of the urine revealed 1+ proteinuria, specific gravity 1.010, and rare granular casts and many white blood cells on the microscopic examination. The phenolsulfonphthalein test yielded 20 per cent excretion in two hours. The non-protein nitrogen was 45 mg. per 100 c.c. of blood and the fasting blood sugar was 80 mg. per 100 c.c. (Studies at another hospital in 1939 had revealed a "normal" non-protein nitrogen and a "normal" phenolsulfonphthalein excretion.) Gastrointestinal roentgen-rays were negative except for "moderate functional stasis." Flat film of the lower abdomen and pelvis revealed "hypertrophic proliferative changes in the region of both femoral greater trochanters." Roentgen-rays of the entire spine revealed advanced osteoarthritic deformities of the last four cervical vertebrae, characterized by anterior and posterior lipping and spurring of the bodies. There was a loss of normal anterior curvature, and a marked left-sided scoliosis of the upper thoracic spine with the apex of maximal convexity at T<sub>8</sub>. There was bony atrophy and minimal lipping of the lumbar vertebrae. Chest roentgenogram revealed arteriosclerosis of the aorta with normal sized heart. There was no pulmonary infiltration. The intravenous pyelogram was within normal limits.

The patient was afebrile during his six-week period of observation. His arthritic complaints were helped greatly by physiotherapy. When he was discharged, he returned to the care of his own physician who continued the use of Ertron, 200,000 units per day. After five more months (10 months since the original onset of vitamin D medication) the patient first noted the appearance of subcutaneous nodules, several of which were painful, involving both wrists and forearms. These gradually increased in size, although the patient believed that several actually became smaller. The arthritic pains of the various joints, especially those of both hands and of the cervical spine, varied in intensity. He entered the hospital on July 11, 1946 because of an increase of his arthritic pain and because of the subcutaneous nodules of both arms. Generalized pruritus, mainly of the trunk, was mentioned on admission. Other medications, besides Ertron, taken by this patient, were a preparation containing vitamin B-complex 3 capsules per day; brewers' yeast, 2 gm. per day; "large doses" of thiamin hydrochloride intravenously; sodium salicylate, 1.5 to 2.0 gm. per day; Metamucil for a period of four months; Pavatrin (anti-spasmodic); and Ventriculin (liver-stomach preparation) for anemia daily for a period of three months; and doses of codeine when needed.

Salient features of the physical examination (July 11, 1946) were: Blood pressure, 145 mm. of mercury systolic and 80 mm. diastolic. Head, eyes, ears, nose and throat were within normal limits. The lungs were clear to percussion and auscultation. The heart was slightly enlarged, the left border extending 2 cm. to the left of the mid-clavicular line. The heart sounds were of good quality. There was a short soft systolic apical murmur. The abdomen was negative. There were bilateral indirect, inguinal herniae. The third left finger was greatly swollen (figure 3). There were between 10 and 15 small, scattered, slightly tender subcutaneous nodules, which varied in consistency from "fibrous" to "calcific." There was marked atrophy of the small hand muscles and lesser atrophy of the muscles of the forearm. There was tenderness over the cervical spine and tenderness and warmth of the finger and wrist joints, but little limitation of motion. Neurological examination was unremarkable.

The patient was placed on a low calcium (100 mg. a day) diet, and Ertron was stopped. He was given aspirin (0.6 gm. four times daily) and codein (0.06 gm. doses as required) for his rheumatoid arthritic pains: Ferrous sulfate (0.2 gm. thrice daily) was given for the secondary anemia. Physiotherapy (whirlpool baths, radiant heat to the spine, and paraffin baths to the hands) was instituted.

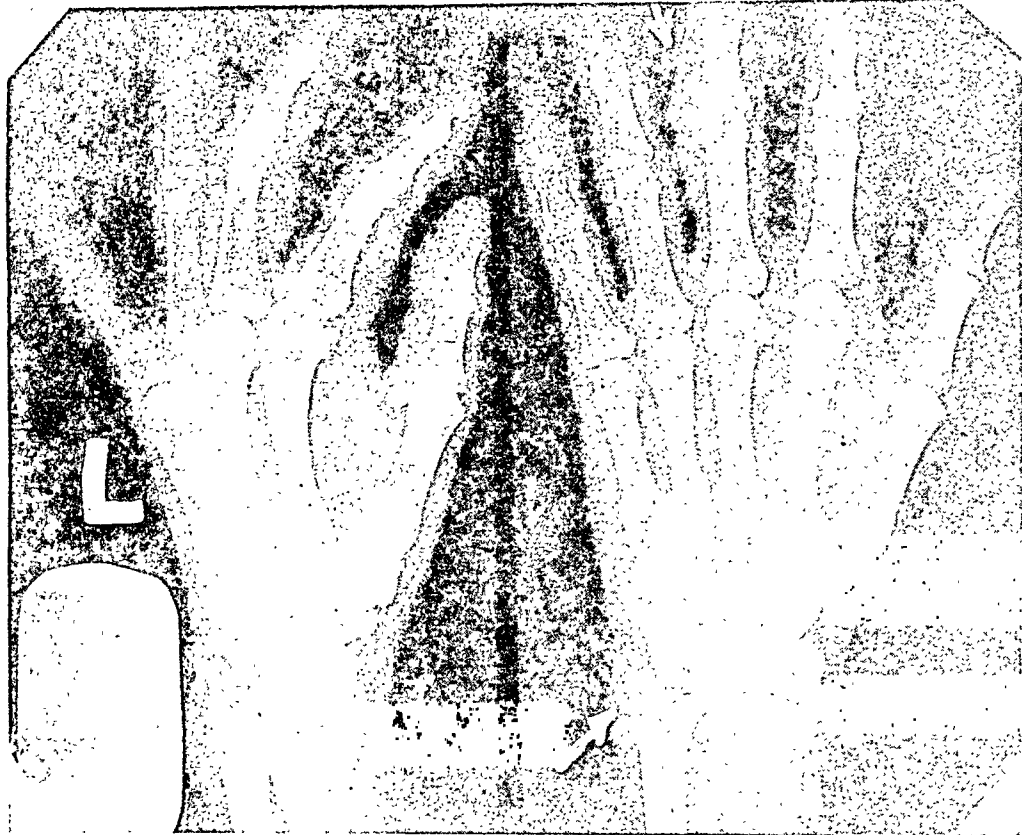


FIG. 4. (*Above*) Roentgen-rays of left hand. Calcification can be seen in the soft tissues of the left third finger and on the ulnar side of the wrist.

FIG. 5. (*Below*) Roentgen-rays of right hand. Note subcutaneous calcification at dorsal and ulnar portions of the wrist.

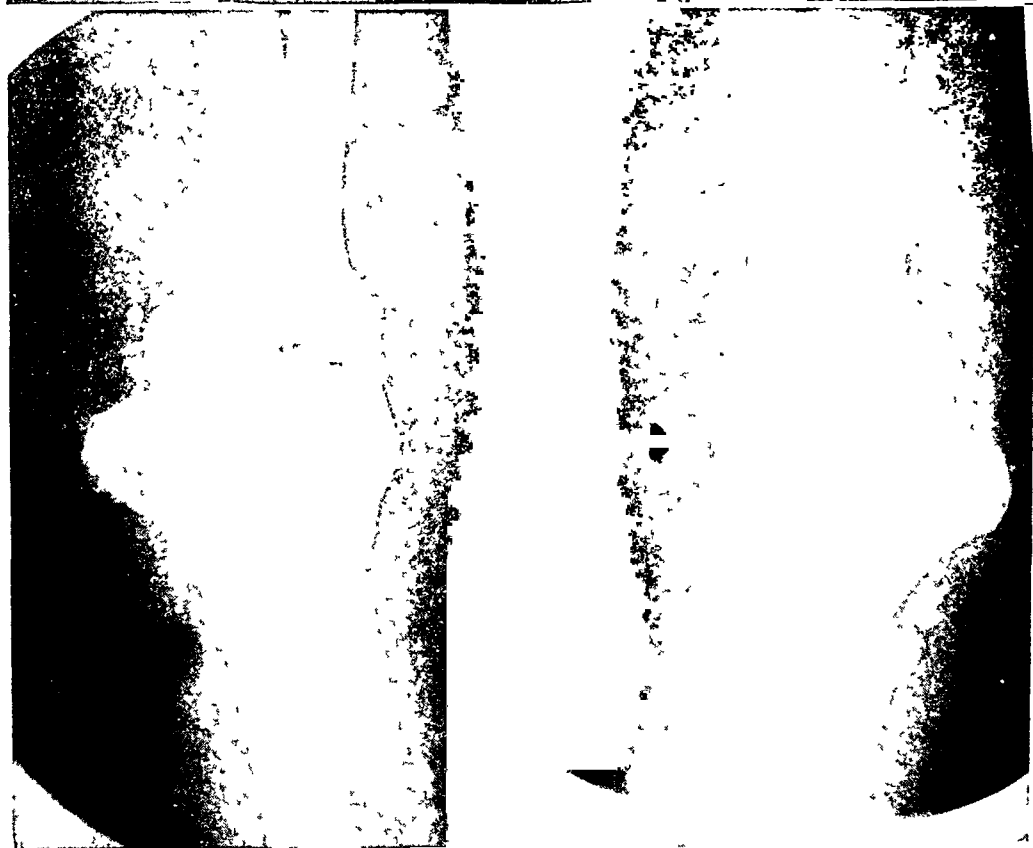
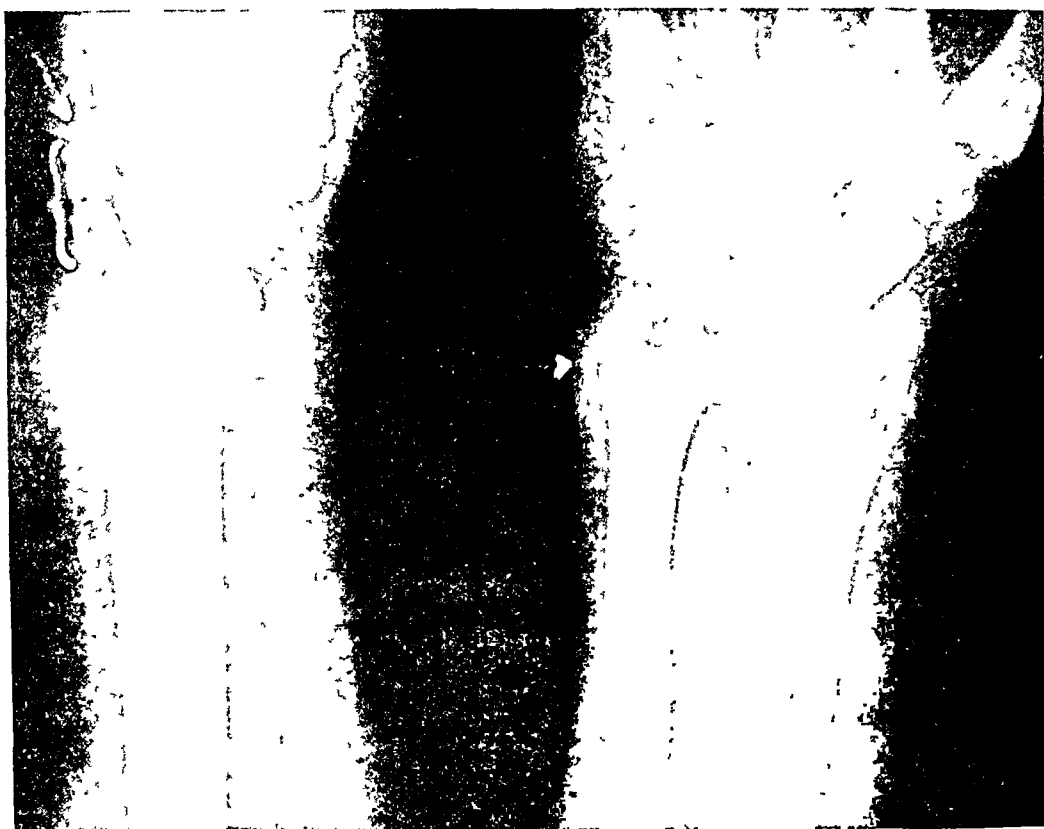


FIG. 6. (*Above*) Roentgen-rays of left hand. Subcutaneous calcification of the wrist.  
 FIG. 7. (*Below*) Roentgen-rays of left elbow. Arrow indicates calcification.

Electrocardiograms were normal. Gastric analysis revealed 2° free HCl in one specimen (after histamine, 0.5 c.c., hypodermically). Sternal marrow puncture was interpreted as revealing a moderate normochromic anemia, with a slight increase in erythropoiesis and no evidence of aplastic changes. Numerous roentgen-rays revealed advanced osteoarthritic changes in the bodies of the lower cervical spine with narrowing of the intervertebral discs between the C-5 and -6 and C-6 and -7; moderate osteoporosis of the thoracic spine; slight sclerosis of the margin of the left sacroiliac joint. A calcified density (5 by 2 cm.) was shown in the right lung (figure 9b); and calcific deposits about both elbow joints (figure 7), ankle joints, phalangeal joints of fingers and toes, near both ischial tuberosities (figure 8), and in the left axilla. A flat film did not show any intra-abdominal calcification.

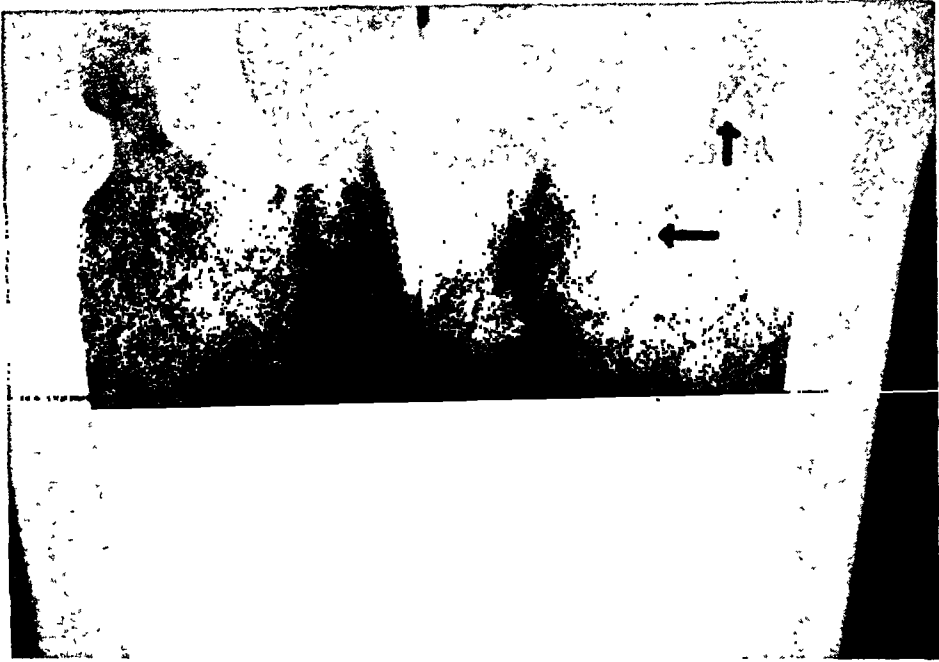


FIG. 8. Roentgen-ray of pelvis. Calcification can be seen.

The laboratory findings are summarized in table 1.

An attempt to biopsy one of the nodules of the right wrist yielded "thick, creamy material," which appeared to be calcific material on smear. Another nodule, which appeared to be a ganglion, was excised from the dorsum of the right wrist. The ganglion was "found to be firmly adherent to the surrounding soft tissue which contained multiple small particles of flaky calcium. The tendon sheaths of the long extensors of the thumb and the index finger were firmly adherent to the ganglion and also contained large quantities of calcium . . . approximately 3 c.c. of milky fluid were obtained from the ganglion" (surgeon's operative note). The ganglion and surrounding soft tissue containing calcium were removed en masse.

The patient's anemia responded well to ferrous sulfate. His rheumatic pains varied with the weather, but usually were not severe. However, codein was required several times weekly for the control of his discomfort and pain. Both the patient and physicians noted the diminution in size of the nodules of the fingers and wrists. Serial roentgen-rays of the hands and wrists revealed a "marked reduction in the periarticular calcification."

TABLE I  
Summary of Laboratory Findings

	1939	Aug. 1945	July 1946	Aug. 1946	Sept. 1946
	(Ertron 200,000 units started January 1945)		(Ertron stopped July 11, 1946 after 17 month's therapy)		
		(7 mos. of Vit. D)			
A. Blood					
1. Non-protein nitrogen (mg./100 c.c.)	"normal"	45	85	52	60
2. Urea nitrogen (mg./100 c.c.)			43	26	30
3. Uric acid (mg./100 c.c.)			3.8	3.6	3.3
4. Creatinine (mg./100 c.c.)				2.4	2.1
B. Serum					
1. Calcium (mg./100 c.c.)			9.3-10.2	10.5-10.7	11.4
2. Phosphorus (mg./100 c.c.)			4.5-4.8	3.5-3.6	3.8
3. Alkaline phosphatase (Bodansky units)			6.5	1.6	4.5
4. Albumin (gm./100 c.c.)			3.5	3.9	4.5
5. Globulin (gm./100 c.c.)			3.0	2.3	2.3
6. Icteric index			10	10	11
C. Blood Counts					
1. Hemoglobin (gm./100 c.c.)		13.1	9.1	12.2	12.5
2. RBC (millions/cu.mm.)		4.0	2.8	4.0	4.1
D. Urine					
1. Albumin		1+	1+	Neg.	Neg.
2. Microscopic		Rare gran. casts; pus	Occas. WBC.	Neg.	Neg.
3. Calcium excretion (mg./24 hrs.)			460	520	610
E. Basal Metabolic Rate			-20%	-13%	-11%
F. Phenolsulfonphthalein Test (Two hour excretion in per cent)	"normal"	20%	45%		35%
G. Concentration and Dilution Test (Maximum concentration)				1011	1012
H. Blood Pressure		145/100	145/80	140/82	144/84

## COMMENT

Increased use of vitamin D has resulted in the publication of numerous reports of vitamin D intoxication. The rationale for the use of a medication (large doses of vitamin D) of doubtful therapeutic value, at best, and of toxic nature, is not clear.

Metabolic study of a patient<sup>12</sup> has revealed that "large doses of vitamin D (Ertron) reduced the fecal excretion of calcium on the low-calcium diet and increased the fecal loss of calcium while the patient was on a high-calcium diet." Vitamin D in large doses is known to cause decalcification of bone, albuminuria, renal insufficiency, hypercalcemia, and metastatic calcification within various tissues and organs. It is important to note that hypercalcemia is not a prerequisite



FIG. 9a. Chest film taken in August 1945 was normal.

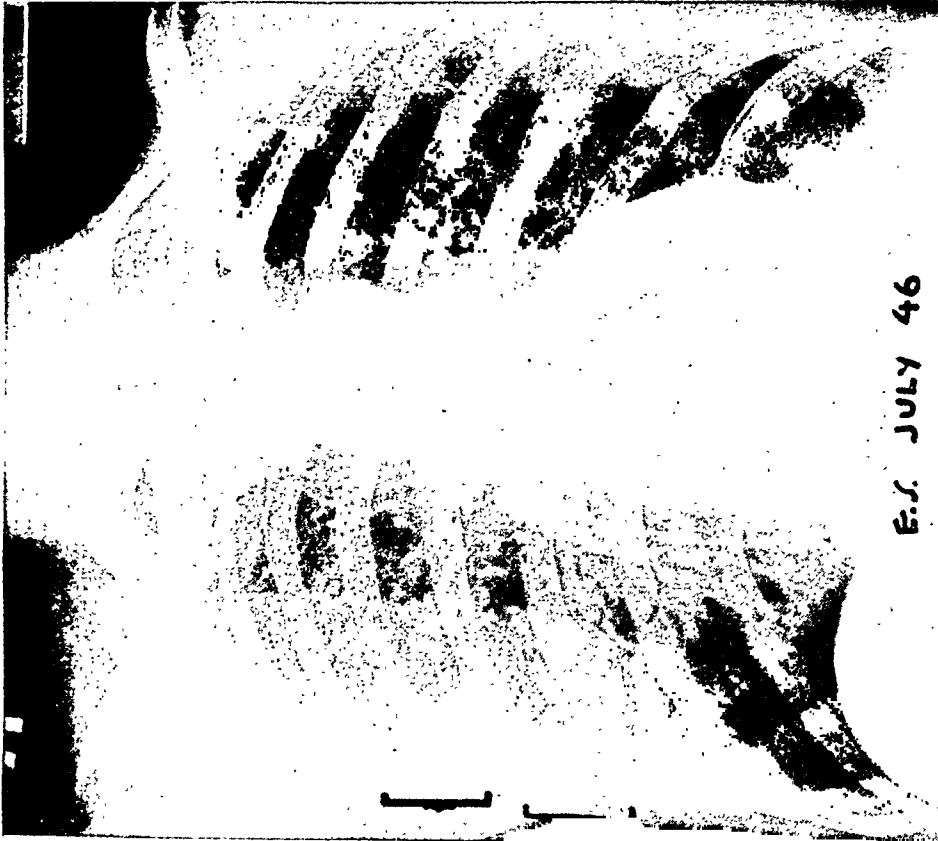


FIG. 9b. In July, 1946, after 17 months of Ertron therapy, calcification can be seen in the right mid-lung field. There are two large areas of calcification. (The upper area is difficult to see in this reproduction.)



to tissue calcification. Freeman et al.<sup>12</sup> emphasize that a high-calcium and phosphorus intake (e.g. 1 qt. of milk daily) increases the toxicity of vitamin D.

### THERAPY

Immediate cessation of vitamin D therapy and a low-calcium diet plus symptomatic care are the mainstays of treatment of the toxic effects of vitamin D. Ashford<sup>8</sup> has noted that the metastatic calcification produced experimentally in rabbits was followed by resorption after vitamin D administration was discontinued. Freeman et al.<sup>12</sup> have reported a case of vitamin D (Ertron) intoxication whose metastatic calcification as shown by roentgenogram diminished six months "after the ingestion of Ertron and high-milk diet had been discontinued."

The patient reported in this paper was placed on a low-calcium diet, and Ertron was discontinued. Within two months, roentgen-rays of the hands and wrists revealed "marked reduction in the periarticular calcification." Pulmonary calcification was unchanged.

### SUMMARY AND CONCLUSIONS

Large doses of vitamin D taken over a period of time may be toxic and can cause metastatic calcification, renal failure, and death. The case reported here is that of a 59-year old white male who received 200,000 units of vitamin D (Ertron) daily for a period of 17 months, and who noted the development of hard, subcutaneous nodules of both arms after 10 months of vitamin D medication. Roentgenograms revealed extensive subcutaneous calcification throughout the body. Despite the absence of renal calcification by roentgen-ray and the absence of hypercalcemia, renal insufficiency was present. Therapy included a low-calcium diet and cessation of vitamin D (Ertron) medication. This resulted in a reduction of subcutaneous periarticular calcification, as seen on roentgen-ray, and symptomatic improvement.

Large doses of vitamin D are of doubtful value in the treatment of rheumatoid arthritis. Concentrated vitamin D medication may be toxic when used over prolonged periods of time.

### BIBLIOGRAPHY

1. FARLEY, R. T., SPIERLING, H. F., and KRAINES, S. H.: A five year study of arthritic patients, *Indust. Med.*, 1941, x, 341-352.
2. SNYDER, R. G., and SQUIRES, W. H.: Follow-up study of arthritic patients treated with activated vaporized sterol, *New York State Jr. Med.*, 1941, xli, 2332-2335.
3. HENCH, P. S., BAUERS, W., CHRIST, B., HOLBROOK, W. P., KEY, J. A., and SLOCUMB, C. H.: The present status of rheumatism and arthritis: review of American and English literature for 1936, *Ann. Int. Med.*, 1938, xi, 1089.
4. ABRAMS, W. R., and BAUER, W.: Treatment of rheumatoid arthritis with large doses of vitamin D, *Jr. Am. Med. Assoc.*, 1938, cxi, 1632.
5. FREYBERG, R. H.: Treatment of arthritis with vitamin and endocrine preparations, *Jr. Am. Med. Assoc.*, 1942, cxix, 1165-1171.
6. WAGNER, L. C.: Evaluation of arthritic cases treated with vitamin D, *Ann. Int. Med.*, 1943, xix, 126-131.
7. Editorial: Irradiated ergosterol—a reminder, *Jr. Am. Med. Assoc.*, 1929, xcii, 2023.

8. ASHFORD, C. A.: The phosphorus distribution in blood and the calcium and phosphorus excretion during hypervitaminosis D, *Biochem. Jr.*, 1930, xxiv, 661.
9. TUMULTY, P. A., and HOWARD, J. E.: Irradiated ergosterol poisoning: report of two cases, *Jr. Am. Med. Assoc.*, 1942, cxix, 233.
10. BOOTS, A. H., cited by COMROE, B. I.: Arthritis and allied conditions, 1944, Lea and Febiger, Philadelphia, pp. 498-499.
11. DANOWSKI, T. S., WINKLER, A. W., and PETERS, J. P.: Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis, *Ann. Int. Med.*, 1945, xxiii, 22.
12. FREEMAN, SMITH, RHOADS, P. S., and YEAGER, L. B.: Toxic manifestations associated with prolonged Ertron ingestion, *Jr. Am. Med. Assoc.*, 1946, cxxx, 197.
13. REED, C. I.: Symptoms of viosterol overdosage in human subjects, *Jr. Am. Med. Assoc.*, 1934, cii, 1745.
14. BAUER, J. M., and FREYBERG, R. H.: Vitamin D intoxication with metastatic calcification, *Jr. Am. Med. Assoc.*, 1946, cxxx, 1208-1215.
15. REED, C. J., STRUCK, H. C., and STECK, I. E.: Vitamin D: chemistry, physiology, pharmacology, pathology, experimental and clinical investigation, 1939, University of Chicago Press, Chicago.
16. HAM, A. W., and PORTUNDO, B. C.: Relationship of serum calcium to pathological calcification of hypervitaminosis D, *Arch. Path.*, 1933, xvi, 1-14.
17. ROSS, S. G., and WILLIAMS, W. E.: Vitamin D intoxication in infancy, *Am. Jr. Dis. Child.*, 1939, lviii, 1142-1143.
18. THATCHER, L.: Hypervitaminosis D with report of a fatal case in a child, *Edinburgh Med. Jr.*, 1931, xxxviii, 457-467.
19. WOLF, I. J.: Safety of large doses of vitamin D in the prevention and treatment of rickets in infancy, *Jr. Pediat.*, 1943, xxii, 707-718.

### STRUMA LYMPHOMATOSA \*

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HASHIMOTO in 1912 described a clinical and pathological entity which consisted of diffuse enlargement of the thyroid in females with evidence of rich infiltration of the thyroid with connective tissue and lymphocytes and lymphoid hyperplasia. This condition not only has been called Hashimoto's disease but also struma lymphomatosa.

Since 1912 it has been debated as to whether this is a distinct clinical entity or a stage of Riedel's struma, as was suggested by Ewing<sup>1</sup> in 1922. Several excellent reviews in the past few years indicate, however, that there is a distinction between struma lymphomatosa and Riedel's struma. Joll<sup>2</sup> in 1939, McSwain and Moore<sup>3</sup> in 1943, Lee<sup>5</sup> in 1935, Clute<sup>8</sup> et al., and others<sup>4</sup> have supported the idea that struma lymphomatosa is a separate clinical entity. In 1943, McSwain and Moore,<sup>3</sup> in a review of the literature, found only 71 cases

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which were reported in sufficient detail to accept as unquestionable struma lymphomatosa.

*Clinical Manifestations.* This condition is found usually between the ages of 40 and 50 and occurs almost exclusively in women. Only three cases have been reported in men. There is usually a firm, diffuse enlargement of the thyroid and mild pressure symptoms such as hoarseness, dysphagia, aphonia, tight feeling in the throat, cough, and substernal pressure. The patients may have myxedematous features such as easy fatigue, mental depression, gain in weight, dryness of the skin, lethargy, etc. However, in rare cases, tremor, nervousness, palpitation, anorexia, fatigue, loss of weight, insomnia, irritability and other symptoms suggesting hyperthyroidism may be present. Schilling<sup>6</sup> states that the symptoms that occur suggesting hyperthyroidism are secondary to the pressure locally and its effect on the sympathetic nervous system, rather than true hyperthyroidism. He also states that the complaints of patients with struma lymphomatosa are always vague with the exception of the goiter and a sense of fullness in the throat. Bothe<sup>7</sup> believes that hyperthyroidism may be associated with struma lymphomatosa, and he presents one case with a basal metabolic rate of plus forty-six. It seems to be agreed, however, that eventually in all cases, hypothyroidism makes its appearance and myxedematous features later appear.

*Etiology.* This condition is a clinico-pathological entity of unknown etiology. Many things have been suggested such as vitamin deficiency,<sup>8</sup> overstimulation of the thyroid by the pituitary thyrotrophic hormone,<sup>10</sup> and, as suggested by Schilling,<sup>6</sup> the possibility of this condition being a degenerative process, in contrast to a neoplastic or inflammatory process. By degeneration it is believed that through the years the gland burns itself out due to the demands of the body. The lymphoid infiltration and hyperplasia that occur are a compensatory and replacement process for the slowly degenerating acini.

*Laboratory Findings.* The laboratory offers very little aid in the diagnosis. The basal metabolic rate may be high or it may be low. Usually it is low and, as the disease progresses, the basal metabolic rate tends to become lower. McSwain<sup>3</sup> mentions also that a relative lymphocytosis may exist.

*Pathology.* In struma lymphomatosa, according to Schilling,<sup>6</sup> the thyroid is diffusely enlarged and may proceed posteriorly and encircle the trachea. The surface of the gland is smooth, pinkish in color, and has a pseudo-lobular appearance. The cut surface appears to be finely lobular with a yellowish cast which is characteristic. There is a diffuse and uniform degeneration of the acini. The epithelium is flattened with eccentrically-placed dark nuclei. The acini shrink, and pale, degenerate cells are seen. The colloid is scant. There are numerous lymph follicles. Plasma cells are occasionally seen. No undue vascularity is noted. There is diffuse infiltration of lymphocytes throughout the gland, in the cells, and between the acini. There is an increase in fibrous connective tissue surrounding the lobules of degenerating acini. This fibrosis increases as the disease progresses. Late in the disease, there may be a complete fibrous replacement of the lobule of the thyroid. This fibrosis is, however, a fine waving type and assumes characteristic waving whorls about the lobules.

*Treatment.* Struma lymphomatosa responds readily to roentgen therapy.<sup>6</sup> A positive diagnosis is essential, and, when the diagnosis is in doubt, a biopsy of the thyroid should be taken before surgery. This is recommended because the progress of the disease is usually toward myxedema, and surgical removal of the

thyroid tissue will only precipitate this condition. If the obstructive symptoms are too marked, or if hyperthyroidism exists,<sup>11</sup> then surgery may have to be done. Following roentgen-ray therapy, the response is rapid and the gland will shrink markedly in size in two or three weeks.

The following is a case report of a patient with struma lymphomatosa. This case presented several interesting features.

#### CASE REPORT

H. F. H., white male, aged 48, occupation clerk, was admitted to the hospital on April 5, 1945. The patient's past history was negative, except for a hemorrhoidectomy

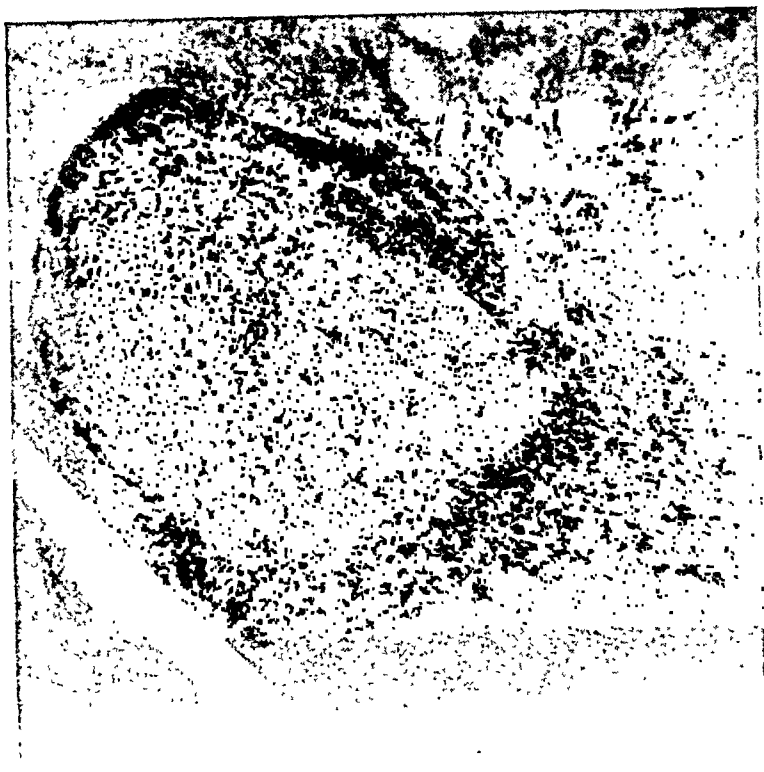


FIG. 1. Section of thyroid showing typical lymphoid hyperplasia with follicle formation.

in 1917, and a herniorrhaphy in 1938. His general health had always been excellent. The onset of the present illness was in February, 1945, when he suddenly became acutely ill with fever and multiple joint pains. The joints were described as being tender, painful, swollen, and with marked limitation of motion. The elbows, knees, and ankles were the chief joints involved. At this time, he was hospitalized in a private hospital where he remained for about one month. He, apparently, became symptom free and was discharged only to have a recurrence of these symptoms in a few days. It was at this time that he came under our observation. In addition to the joint symptoms, the patient complained of nervousness, choking sensation, difficulty in swallowing, loss of 10 to 15 pounds of weight, restlessness, irritability, free perspiration, and a low grade fever. He stated that he preferred cold weather to hot weather. His appetite had been good and no diarrhea had been noted. The remainder of the history was not contributory.

On physical examination, the patient was found to be well developed and he did not appear acutely ill. He was quite nervous, and during the initial interview he constantly twisted and turned in his chair, and would wring his hands frequently. There was advanced pyorrhea of the gums. There was no exophthalmus, lid lag, stare, or lack of convergence of the eyes. A definite fine tremor of the eyelids, tongue, and outstretched fingers was observed. The thyroid gland was enlarged and this appeared to be more noticeable on the right side of the neck. The thyroid was firm and appeared diffusely enlarged and the trachea was not deviated. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic and the pulse rate was 96. The heart was



FIG. 2. Section of thyroid showing diffuse and localized lymphoid infiltration with some thyroid pressure atrophy.

negative, except for a short systolic murmur at the apex. There was limitation of motion due to pain in the right shoulder but no external evidence of swelling or increased local heat about the joint was noted. The remainder of the joints, at this time, were negative. A small inguinal hernia was found on the right side. The physical examination was otherwise not remarkable.

The laboratory studies showed the urine to be negative. A smear for malaria was negative. The red blood count was 4,350,000 with a hemoglobin of 16 grams. The white blood count was 8400 with 64 per cent polymorphonuclear cells, 23 per cent lymphocytes, and 3 per cent monocytes. The Kahn, Kline, and Wassermann tests were negative. The sedimentation rate was 20 mm. in one hour. A throat culture

was negative. Roentgen-rays of the elbows, left knee, and left ankle were negative. The roentgen-ray of the heart and lungs was negative. The electrocardiogram showed sinus tachycardia but was otherwise negative. Agglutination for undulant fever, typhoid, paratyphoid A and B, and proteus X-19 were all negative. Basal metabolism tests were attempted on several occasions, but the patient would become apprehensive and complain of choking and smothering each time the test was attempted. Blood cultures were negative.

At the time of admission the patient was placed on bed rest, salicylates, multiple vitamins, a high caloric and a high vitamin diet. He continued to have acute involvement of various joints with redness, swelling, increased heat and pain all being present, in addition to a low grade fever. He was tried on a therapeutic course of sulfadiazine, but he received no appreciable benefit. Due to the pyorrhea of the gums, and evidence of oral caries, his remaining teeth were extracted in an attempt to clear up this possible focus of infection. In spite of the above therapeutic approach, the patient continued to run a low grade fever, lose weight, complain of weakness, nervousness, palpitation, choking sensations in the throat and smothering spells. His pulse was consistently elevated, with a rate as rapid as 140 at times recorded. Attempts were again made to get a basal metabolism test, and, finally, a recording of plus 69 was obtained. It was not believed to be a satisfactory test due to the inability of the patient to cooperate. The joint symptoms had subsided, and after observation by both the medical and surgical services, it was decided to place the patient on Lugol's solution and, if he responded clinically, surgical removal of the thyroid would follow. After Lugol's solution was administered, it was noted that the patient was improved and on August 13, 1945, a subtotal thyroidectomy was performed. The thyroid was two and one-half times normal size at operation. It was dense, firm, and hyperplastic in appearance. A few nodulations were noted in the right lobe, but the thyroid appeared to be diffusely involved. The pathologic report is as follows:

Gross: Specimen consists of two lobes of thyroid tissue, one measuring 6 by 5 by  $3\frac{1}{2}$  cm., the other 7 by  $5\frac{1}{2}$  by 4 cm. in diameter. Both lobes are surrounded by well formed capsules. The surface is irregularly nodular and moderately firm in consistency. The cut surface of the thyroid is dullish gray in color with scattered, grayish-white, small nodules varying up to 1 mm. in diameter. In a few areas there is suggestive increase in the connective tissue. Histological examination of sections of the thyroid tissue shows areas of normal thyroid acini completely filled with collagenous colloid. The lining epithelium is low cuboidal. There is no evidence of hyperactivity of the gland. In many areas there is a diffuse, lymphocytic infiltration crowding out the thyroid tissue. In other areas there is definite lymph follicle formation with large germinal centers. In these areas there is pressure atrophy of the surrounding thyroid tissue. Scattered through these areas are also some slight increases in the interstitial connective tissue. In view of the diffuse overgrowth of lymphoid tissue and the formation of lymph follicles containing large germinal centers, as well as the slight increase in the connective tissue, it appears that we are dealing with a struma lymphomatosa.

In view of the fact that this is a rare disease, the microscopic sections were referred to N. Chandler Foot<sup>12</sup> for review. He stated that they were in every way typical of struma lymphomatosa. He also stated he had seen only two previous cases in male patients.

The postoperative course was complicated by an acute exacerbation of the joint symptoms with the right hand, right wrist, right elbow, and right knee being swollen, red, and painful. There was an accompanying rise in temperature to 102°. He developed a cough and expectorated mucopurulent material. A roentgen-ray of the chest on the second postoperative day showed an area of

cloudiness in the midportion of the right lung along the periphery. The patient was placed on penicillin and his fever and clinical symptoms slowly abated. He became symptom free, began to gain weight, and reached a peak of 167 pounds before his discharge. His weight had dropped to 146 pounds prior to surgery. His nervousness decreased and he improved. He was discharged on October 11, 1945.

Since discharge it is reported that this patient is working daily and at present has no symptoms indicative of hypothyroidism or of myxedema.

### SUMMARY

1. A review of the clinical manifestations, etiology, laboratory findings, pathology, and treatment of struma lymphomatosa is presented.

2. A case report of struma lymphomatosa occurring in a white male, with clinical evidence of hyperthyroidism, is also presented. The occurrence of this condition in males is very rare. The presence of symptoms suggesting hyperthyroidism, as noted in this patient, is not the usual clinical picture.

3. The difficulty in establishing the diagnosis without microscopic sections of the thyroid is clearly demonstrated in this case.

### BIBLIOGRAPHY

1. EWING, JAMES: Benign granuloma of the thyroid, Riedel's struma. *Neoplastic Diseases*, 3d ed., 1928, W. B. Saunders, Philadelphia, 961.
2. JOLL, CECIL A.: Pathology, diagnosis and treatment of struma lymphomatosa, *Brit. Jr. Surg.*, 1939, xxvii, 351-389.
3. McSWAIN, BARTON and MOORE, S. W.: Struma lymphomatosa, *Surg., Gynec. and Obst.*, 1943, lxxvi, 562-569.
4. GRAHAM, A., and McCULLOUGH, E. P.: *Arch. Surg.*, 1931, xxii, 548-567.
5. LEE, J. GORDON: Chronic nonspecific thyroiditis, *Arch. Surg.*, 1935, xxxi, 982.
6. SCHILLING, J. A.: Struma lymphomatosa, struma fibrosa and thyroiditis, *Surg., Gynec. and Obst.*, 1945, 533-549.
7. BOTHE, F. A.: Riedel's struma and struma lymphomatosa, *Clinics*, 1944, iii, 215-220.
8. CLUTE, H. M., ECKERSON, E. B., and WARREN, S.: Struma lymphomatosa, *Arch. Surg.*, 1935, xxxi, 419-428.
9. McCARRISON, R.: Struma lymphomatosa, *Brit. Med. Jr.*, 1929, i, 5-6.
10. HELLWIG, C. A.: Lymphadenoid goitre, *Arch. Path.*, 1938, xxv, 839-849.
11. SCARALLO, N. S., and GOODALE, R. H.: Struma lymphomatosa, case complicated by myxedema, *New England Med. Jr.*, 1941, ccxxiv, 60-64.
12. FOOT, N. CHANDLER, Surgical Pathologist to the New York Hospital: Personal Communication.

### PRIMARY LYMPHOSARCOMA OF THE LUNG (A CASE REPORT AND REVIEW OF THE LITERATURE) \*

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THE medical literature contains many references to sarcoma of the lung. These may originate in connective tissue or lymphoid tissue. However, previ-

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ously reported tumors have always shown involvement of other structures than lung, usually the mediastinal lymph nodes. Thus, it has been difficult to say where the tumor arose. Falconer and Leonard<sup>1</sup> reported a series of 25 cases of lymphosarcoma of the lung and mediastinum. None of these involved the lung alone. Cutler<sup>2</sup> reported a series of 30 cases of lymphosarcoma, one of which was lymphosarcoma of the lung. However, no microscopic description was given and there was no indication of its being limited to, or primary in, the



FIG. 1. Photograph of lower lobe of right lung showing the tumor mass cut across.

lung. O'Donnell<sup>3</sup> reported two cases of lymphosarcoma of the lung. Both of these showed involvement of tissue other than lung and may well have originated in the mediastinum. Peters<sup>4</sup> reported 13 cases of sarcoma of the lung and mediastinum; no microscopic description was included in the report.

A case of lymphosarcoma was described by Pekelis.<sup>5</sup> Microscopic description revealed it as a "small cell" lymphosarcoma arising from the peribronchial lymphoid tissue of the lung. Grossly, the tumor was a large mass the size of a small orange infiltrating the lower lobe of the left lung. It was hard and nodular and yellow-pink in color. There were metastases in the sternum, in the fourth and fifth right ribs and in the liver. The mediastinum and other thoracic structures were not involved.



The case presented herewith is one in which the lesion is limited to the lower lobe of one lung. There is no doubt of its origin in the lung, since no other structures in the body are involved. The case reported by Pekelis<sup>5</sup> is the one other case in the literature in which the sarcoma can definitely be said to originate in the lung.

#### CASE REPORT

The patient, a 34 year old white female, was admitted October 7, 1944 to the Jewish Hospital of Brooklyn on the service of Dr. Rudolph Nissen with a history of



FIG. 2. Low power photomicrograph showing a collar of tumor cells about a bronchus.  
H & E.  $\times 10$ .

hemoptysis for three months and occasional right chest pain for the same period of time. The family history was negative.

In July 1944, patient noted blood streaked sputum. She had no real chest pain but felt some slight discomfort in the chest. She had a moderate cough for three months preceding admission. Roentgen-ray before admission revealed a small egg-shaped mass in the right chest.

On physical examination there was an area of slight dullness below the angle of the right scapula and in the right base with occasional rhonchi and medium moist râles. Sedimentation rate was 77 mm. per hr.; otherwise the laboratory findings were not remarkable. Bronchoscopy on October 11, 1944 revealed evidences of suppuration in the lower lobe of the right lung. Roentgen-ray, October 16, 1944, revealed an area of homogeneous opacity in the lower right pulmonic field peripherally, which was suggestive of encapsulated fluid. In lateral view, the lesion was confined to the right lower lobe posteriorly. In this view, the lesion had a mottled appearance.

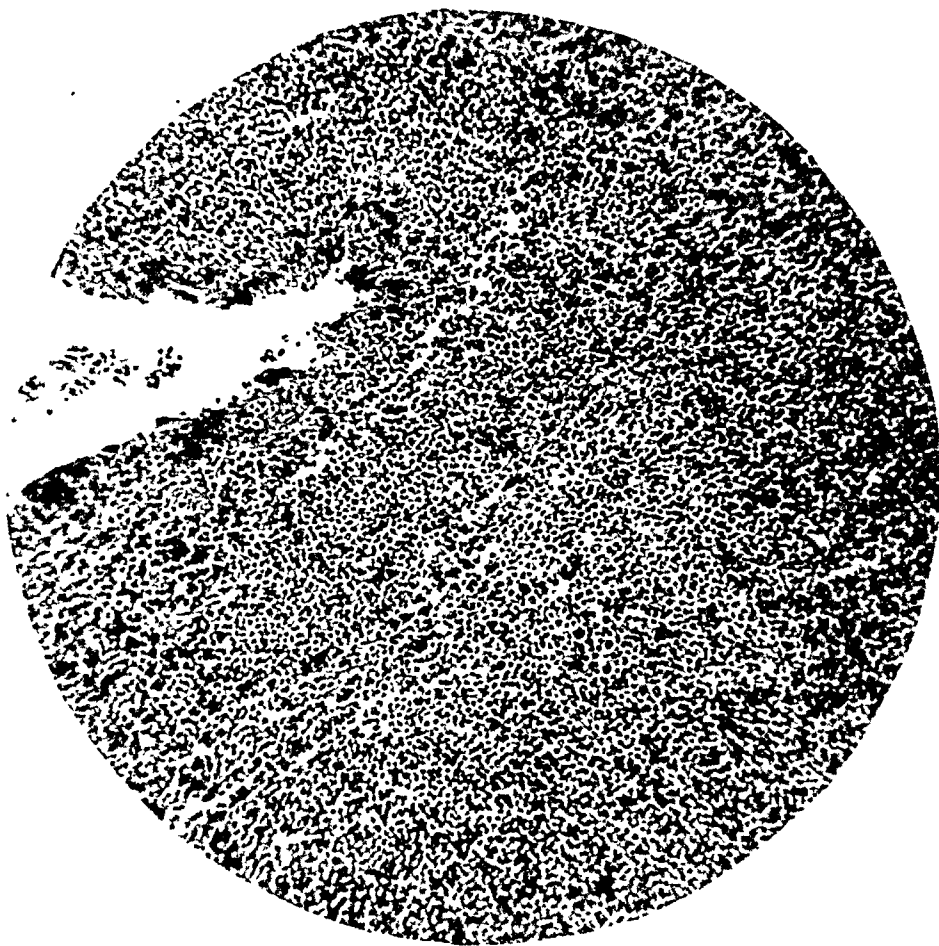


FIG. 3. Low power photomicrograph showing general cytoarchitecture of the tumor infiltrating wall of a bronchus at lower edge. H & E.  $\times 100$ .

On October 20, 1944, the patient was discharged with a diagnosis of lung abscess to be treated with penicillin at home. The patient was again admitted to the hospital January 21, 1945 (three months later). Her condition had remained about the same during the interval and she had gained 10 lbs. At this admission she complained of cough, bloody sputum and occasional gnawing pain in the right anterior chest.

On physical examination her blood pressure was 128 mm. Hg systolic and 82 mm. diastolic, the breath sounds were increased throughout posteriorly and there were occasional evanescent fine râles at the angle of the right scapula.

Roentgen-ray of the chest on January 22, 1945 showed an area of opacity at the right base posteriorly. On lateral view, it was not homogeneous. There was an area of infiltration within which there may have been necrotization, but a definite fluid level was not demonstrated. On the lateral view, there were two nodular opacities, one just below the root and the other slightly anterior to the infiltrated area.

The patient was operated on January 26, 1945 and the lower lobe of the right lung was removed.

The post-operative roentgen-rays on nine occasions revealed a hydropneumothorax with slowly expanding upper and middle lobes of the right lung.

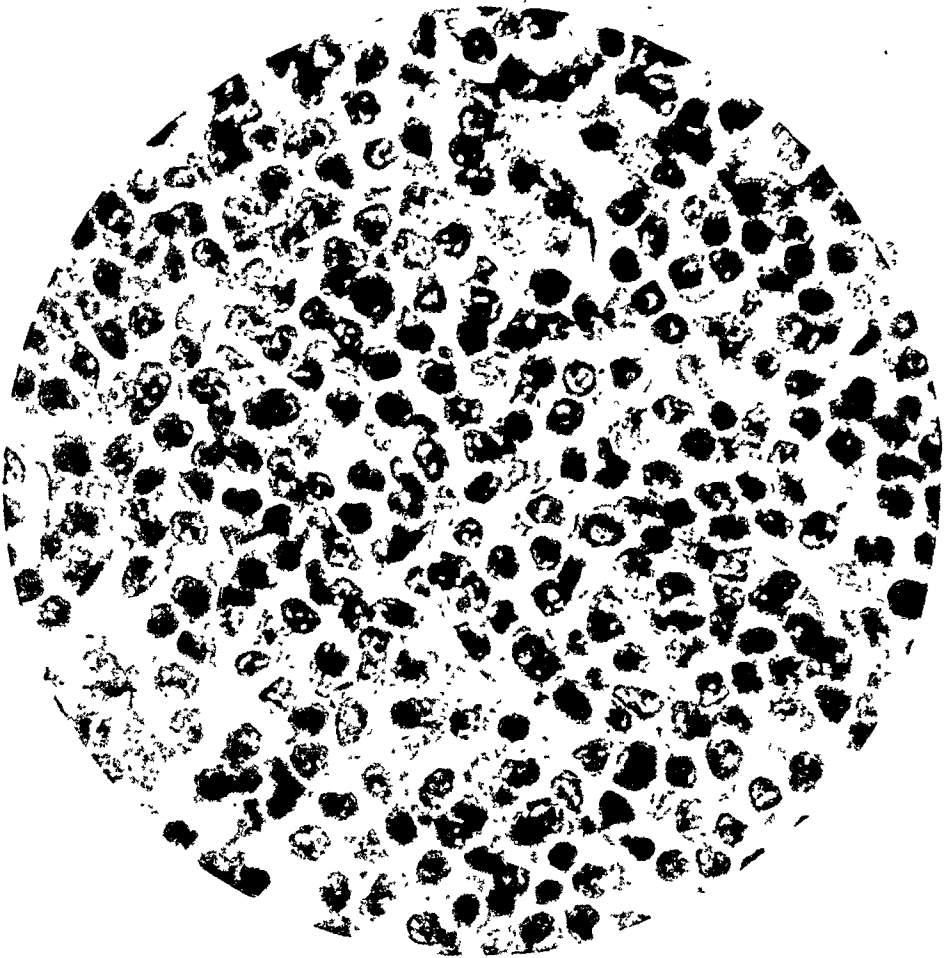


FIG. 4. High magnification of tumor cells. H & E.  $\times 400$ .

Urine and blood examinations were not significant. Sedimentation rate was 83 mm. per hr. On March 25, 1945, the patient was discharged with the diagnosis of lymphoblastoma (lymphosarcoma) of the lung and empyema thoracis, post-operative.

#### PATHOLOGY

*Gross Description:* The specimen consisted of the lower lobe of the right lung. It measured 17 by 11 by 3.5 cm. The external surface was purple red and gray pink

with a reticular gray white pattern. It was smooth and glistening except in several small areas where it was roughened by fibrous tissue tags. In the central portion an irregular egg-shaped moderately firm mass was palpated and the surrounding lung tissue was subcrepitant. On cut section, a good portion of lung tissue was replaced by moderately firm gray white, pink gray, and gray yellow tissue. It occupied an irregular area measuring 7 cm. in greatest diameter. The borders faded imperceptibly into the surrounding lung tissue. A bronchus measuring 0.9 cm. in diameter extended into the mass and fused with it. The lung tissue was pink gray and in places there were small bronchiectatic cavities.

*Microscopic Description:* The striking picture in preparations from various portions of the lung through the tumor mass was the collar of cells about bronchi and bronchioles and to a lesser degree about the blood vessels. In many of the bronchioles the lining cells were partly or completely desquamated, and some contained a purulent exudate. The tumor cells were of large round cell variety. Many were lymphoblasts and a few showed mitotic figures. In all the preparations, the cells about the lining bronchial epithelium merged with the sheets of cells forming the collar about them. These tumor cells were also seen in places extending along the septa to the deeper portions. The alveolar spaces in places contained foam cells and mononuclear cells with pigment granules, as well as polymorphonuclear leukocytes. The cartilage plates about the larger bronchi appeared compressed. Some areas showed atelectasis while others showed compensatory emphysema. Foci of extravasated blood were also present.

*Diagnosis:* Lower lobe of right lung with lymphoblastoma (lymphosarcoma).

#### DISCUSSION

Lymphosarcoma, primary in the lung, is a rare lesion. Lymphoid tissue, from which lymphosarcoma arises, is widely distributed throughout the body and is particularly abundant in the mediastinum. Most of the reported cases of lymphosarcoma of the lung involved mediastinal or other thoracic tissues. It is very likely that these reported tumors arose in lymphoid tissue outside the lung and only secondarily involved the lung. Only one case was seen in the literature where it can definitely be said that the lymphosarcoma originated in the lung. The case reported above is one of the rare cases in which the lesion is so situated anatomically, that at operation or autopsy, it can be said definitely to have arisen in the lung. Obviously, the case must have been seen early in its course since it involved only one lobe of the lung and no other tissue. Peters<sup>4</sup> concluded, after reporting 13 cases of lymphosarcoma of the lung and mediastinum, that it is difficult to say which is involved first, the lung or mediastinum, unless the case is seen early. He further concluded that the mediastinum is more often the original seat of the growth.

As a further indication that only the lung was involved, the patient is alive and well 14 months after operation, with no evidence of metastasis or extension at this time.

#### BIBLIOGRAPHY

1. FALCONER, E. H., and LEONARD, M. E.: Pulmonary involvement in lymphosarcoma and lymphatic leukemia, *Am. Jr. Med. Sci.*, 1938, *cxcv*, 294-301.
2. CUTLER, M.: Lymphosarcoma (a clinical, pathological and radiotherapeutic study with a report of 30 cases), *Arch. Surg.*, 1935, *xxx*, 405-441.
3. O'DONNELL, T. J.: Two cases of lymphosarcoma of the lung, *Irish Jr. Med. Sci.*, 1926, 324-326.

4. PETERS, C. A.: Primary sarcoma of the mediastinum and lungs, *Med. Clin. N. Am.*, 1924, vii, 1823-1842.
5. PEKELIS, E.: Peribronchial lymphosarcoma with rapid intrapulmonary development, *Pathologica*, 1931, xxiii, 66-71.

## CERVICAL ACTINOMYCOSIS WITH EMBEDDED FOREIGN BODY AND WITHOUT SINUS FORMATION \*

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CERVICOFACIAL actinomycosis is the most common type of this disease and the type which is most readily amenable to combined medical and surgical treatment. No attempt is made to review the literature; this case is presented because it is interesting, and unusual in that an embedded foreign body was present and no sinus formation developed.

### CASE REPORT

A 30 year old private was admitted to Army Hospital on November 8, 1945 complaining of painless swelling of the glands in the left side of his neck.

Family History: Non-contributory.

Past History: Patient was born and reared in East Orange, N. J.; and lived there all his life before entering the army. He had the usual childhood diseases and scarlet fever without sequelae. He had always enjoyed excellent health. He had been married for 10 years and had five children.

Present Illness: While on maneuvers in early August 1945, near Camp Claiborne, La., he dived into a pile of hay and a long piece of straw entered his mouth. He immediately pulled the straw out, but felt that a small piece had remained embedded under his tongue on the left side. The straw abraded his throat but this healed after four or five days. He reported to the doctor immediately after the accident and no foreign body was found in his mouth. Ten days after the injury he first noticed swelling in the left side of his neck. This was painless and not red and he had no constitutional symptoms. The swelling gradually increased and on November 8 he was admitted to the Regional Hospital at Ft. Jackson, S. C. He was under observation in this hospital for seven weeks, and during this period of time the swelling in the left side of the neck gradually increased. Late in November 1945 he again had the sensation that some foreign body was present in the left side of his neck but no lesion of the mucous membrane was found.

Early in December the skin over the swelling on the left side of the neck became red and he was treated with penicillin from December 10 to 13 receiving 30,000 units every three hours. The swelling decreased somewhat and the redness subsided. He was transferred to Oliver General Hospital on December 17, 1945.

Physical examination on December 18 showed temperature 97.8°, pulse 74, respirations 16, weight 172 lbs. and blood pressure 115 mm. Hg systolic and 70 diastolic. Patient was a well developed, well nourished, healthy looking man. There was a hard brawny mass in the left submandibular area extending down to the supraclavicular region. The overlying skin was red and attached to the underlying tissue. There

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was no definite fluctuation and no lymph nodes could be definitely and distinctly palpated. Trachea was displaced slightly to the right. Head, eyes, ears, and nose were normal. Direct laryngoscopy showed nothing abnormal. Lungs were clear. Heart was normal. Abdomen, genito-urinary tract, and glandular systems were negative. Muscular system was well developed. Neurological examination was normal. There was no abnormality of the bones or joints.

Laboratory studies showed hemoglobin 94 per cent; red blood cell count 4.58 million; white blood cell count 7,000 with 65 per cent neutrophiles, 26 per cent lymphocytes, 6 per cent monocytes, and 3 per cent eosinophiles. The sedimentation rate was 28 mm. per hour (Wintrobe). Kahn test was negative. Urinalysis was normal. Tuberculin test was positive with second strength P.P.D. A roentgenogram of the chest was negative. Roentgen-rays of the soft tissue of the neck showed no foreign body and no calcification.

On December 18, 1945, patient was started on sulfadiazine 4 grams daily, penicillin 40,000 units every three hours, and saturated solution of potassium iodide 0.5 gram three times a day after meals, and this treatment was continued until operation on January 10, 1946. During this time he had no untoward symptoms from the drug therapy and the swelling in the left side of the neck definitely decreased. There was much less induration and now numerous hard lymph nodes were palpable. He was then seen by the surgical consultant who felt that operation was indicated. He had no fever except for a slight elevation from January 3 to 5 when he had an acute upper respiratory infection. He still had no constitutional symptoms. Sulfadiazine levels in the blood ranged from 6.6 to 14.3 mg. per cent.

Operation: On January 10, 1946 under a gas-oxygen-ether anesthesia, the mass on the left side of the neck was excised. Enlarged matted glands were found just lateral to the thyroid notch both superficial and deep to the leading margin of the sternocleidomastoid muscle. The glands were removed in two sections; considerable difficulty was encountered because the glands were densely adherent to the adjacent muscle. At the innermost and deepest part of the operative field, a piece of straw 1 cm. in length was encountered and removed. This straw appeared to be coming directly from the tonsillar region. The bleeding points were tied and a rubber tissue drain was inserted in the wound. The subcutaneous tissues were closed with interrupted sutures of No. 80 cotton. The skin was closed with black silk and the patient was returned to the ward in good condition.

Penicillin 40,000 units every three hours was continued after operation until January 16, 1946. Sutures and rubber drain were removed from the incision on January 17 and the wound healed by first intention. Patient was then put on sulfadiazine and potassium iodide in the same dosage as before and this was continued until March 10, 1946. The induration in the neck gradually subsided and the patient remained asymptomatic and afebrile. Pathological examination of the tissue removed at operation showed numerous actinomyces granules with characteristic marginal clubs, surrounded by numerous neutrophiles, mononuclears, and fibrous tissue.

After several weeks' post-operative stay in the hospital, the patient was sent on a 30 day convalescent furlough. When he returned his neck was soft and pliable, there was no redness, and no palpable glands. Apart from the scar, which was placed in a fold and was therefore relatively unnoticeable, the neck appeared to be normal. He gained weight and the sedimentation rate was 12 on March 21, 1946. By private correspondence, the patient reported himself completely well five months after operation.

*Summary:* A 30 year old man who developed cervical actinomycosis 10 days after injuring the mucous membrane of his oro-pharynx with a straw was treated with penicillin, sulfadiazine, potassium iodide, and surgical excision four

months after onset. There was no sinus formation; a straw 1 cm. in length was found embedded in the diseased tissue. The patient is apparently cured five months after operation.

### DISCUSSION

This patient gave a definite history of a foreign body (straw) entering and embedding itself in his oro-pharynx, and he was not sure that all of the straw had been recovered and removed. Several times during the course of his illness, he felt as if there was "something sticking" in the left side of his neck. No one felt that this sensation was due to a foreign body before the straw was found at operation.

After operation, the sensation did not recur and in retrospect, it seems probable that the foreign body had caused the feeling of "something sticking" in his neck. The straw apparently had entered the soft tissues of the neck through the tonsil, since it was found embedded in the tonsillar area during the excision of the diseased tissue.

The fact that no sinus formation developed is very unusual in actinomycosis. The presence of this fungus infection was at once considered likely after a complete history was obtained. Although actinomycosis could not be proved before operation, treatment with penicillin, sulfadiazine, and potassium iodide was started at once. This massive chemotherapy may well have aborted the formation of skin sinuses. Before chemotherapy was started, the involved area was comparatively soft but not fluctuant, and there were no breaks in the skin. During chemotherapy, the soft area gradually decreased in size and became very firm.

After three weeks of medical treatment, it seemed obvious that further change in the involved tissue could not be expected. Surgical treatment was considered necessary and the eventual course of the patient vindicated this decision.

### SUMMARY

1. Actinomycosis may be present without sinus formation and with an embedded foreign body.
2. The importance of combined medical and surgical treatment is stressed.

## EDITORIAL

### THE THERAPEUTIC USE OF NITROGEN MUSTARDS

THE sulfur and nitrogen mustards, because of their use as warfare agents, have been subjected to intensive study, both as to their chemical nature and their action on the tissues. Although originally employed primarily because of their local irritant and vesicant action on the skin and mucous membranes, it was soon recognized that when absorbed they exert a toxic action on a variety of tissues.

In animals subjected to toxic doses,<sup>1</sup> the tissues most severely involved are the mucosa of the gastrointestinal tract and the hemopoietic tissues. There is vacuolization and swelling of the nuclei of the gastrointestinal epithelium, followed by necrosis and desquamation. This is accompanied by severe nausea, vomiting and diarrhea. There is loss of body fluid and electrolytes, which leads to shock and circulatory collapse which is quickly fatal in severe cases. There is also disintegration and destruction of the lymphoid tissues throughout the body and of the hemopoietic cells in the bone marrow, which in less rapidly fatal cases leads to almost complete aplasia of these tissues.

It has been shown that when administered in sublethal threshold doses, the action of these mustards is largely confined to those tissues which normally proliferate rapidly. The first objective evidence of injury is an inhibition of mitotic activity and cellular multiplication. This may occur without other evidence of injury to either the nucleus or cytoplasm of the cell. Experiments with *Tradescantia* pollen and with fruit flies (*Drosophila*) have shown that exposure to mild concentrations of the mustards may cause translocations and other abnormalities of the chromosomes which may be transmitted through successive generations, like those induced by radiation.

Although the toxic action of these substances appears to affect the nucleus primarily, in special instances evidence of probably independent injury to the cytoplasm has been obtained.

The mechanism of the toxic action of the mustards has not been entirely elucidated. The activity of these compounds is attributed to a chemical change which takes place when they are put in aqueous solution, an intramolecular cyclization with formation of a highly reactive onium cation and liberation of Cl<sup>-</sup>.<sup>1</sup> It has been suggested that cell injury is brought about by interference with the enzyme systems of the cells. There is experimental evidence that the mustards do powerfully inhibit the activity of certain enzymes, particularly the phosphokinases, although many other systems are little affected. Mitosis may be inhibited, however, by concentrations of

<sup>1</sup> GILMAN, A., and PHILLIPS, F. S.: The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides. *Science*, 1946, ciii, 409-415.



mustards which are below those which are required to affect tissue respiration or glycolysis under experimental conditions.

The capacity of the mustards to inhibit mitotic cell division and their relatively selective action on hemopoietic tissue naturally suggested that they might have therapeutic value in neoplastic diseases, particularly in lymphomata and in the leukemias. Preliminary experiments with animals gave sufficiently promising results to warrant a trial in man. The use of these drugs clinically in this country has thus far been restricted to several qualified institutions to which the material has been supplied by the Committee on Growth of the National Research Council.

The sulfur mustards have been regarded as too highly reactive and toxic for therapeutic use, and the experiments thus far reported have been restricted to the use of two nitrogen mustards, *tris*(beta-chloroethyl) amine hydrochloride and methyl *bis*(beta-chloroethyl) amine hydrochloride. The latter compound has been more extensively used since it appears to be significantly less toxic than the former and equally effective.

These drugs are readily soluble in physiological salt solution. They are intensely irritating to the tissues and must be given intravenously and without leakage. To lessen the tendency to thrombosis it is customary to start an intravenous infusion of saline or glucose solution, and when this is flowing in rapidly to introduce a measured quantity of the drug into the system by piercing the rubber tubing with a hypodermic needle and rapidly injecting the solution. As the drugs speedily undergo chemical change in solution and presumably their effectiveness may thereby be altered, they must be administered immediately (within five minutes) after the solution is prepared. The customary single dose is 0.1 mg. per kilogram of body weight (maximum 8 mg.), and this dose is usually administered on four consecutive days (occasionally six or seven doses have been given). In case of relapse subsequent courses of two to four doses have been given, usually only after an interval of six to eight weeks. The administration of doses twice this size to a few patients has resulted in excessive and alarming depletion of the marrow, although recovery has been almost invariable.

Thus far reports of treatment of about 150 patients have been published (Goodman et al.,<sup>2</sup> 67 cases; Jacobson et al.,<sup>3</sup> 59 cases; ApThomas and Cullumbine,<sup>4</sup> 25 cases). A preliminary summary of the results obtained in the earlier cases treated in this country was published by Rhoads.<sup>5</sup> Although this number is relatively small, it permits some tentative conclusions as to the probable effectiveness and limitations of these drugs.

<sup>2</sup> GOODMAN, L. S., et al.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 126-132.

<sup>3</sup> JACOBSON, L. O., et al.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 263-271.

<sup>4</sup> AP THOMAS, M. I. R., and CULLUMBINE, H.: Nitrogen mustards in Hodgkin's disease, Lancet, 1947, i, 899-901.

<sup>5</sup> RHOADS, C. P.: Nitrogen mustards in the treatment of neoplastic disease, Jr. Am. Med. Assoc., 1946, cxxxii, 656-658.

In nearly all cases nausea and vomiting follow the injections within two to four hours and last for several hours, rarely for 24 to 48 hours. Exceptionally there may be diarrhea and a more protracted anorexia.

Effective doses almost invariably cause some depletion of the hemopoietic tissues. This is the limiting factor in determining dosage. The margin between an effective dose and a seriously toxic dose is narrow. This injury may be evident within 24 hours as shown by a fall in the total leukocyte count and by the presence in blood films of cells showing morphological evidence of degenerative changes, particularly in the nuclei. Both lymphocytes and neutrophilic granulocytes are severely affected; observations as to which are first affected are conflicting, and this probably varies in different cases. There is usually a progressive leukopenia reaching a minimum count of 1000 to 5000 after two to three weeks. There is then a recovery to normal figures within about two weeks, associated with a shift to the left in the granular leukocytes and often the appearance of some myelocytes in the circulating blood. In a few cases, particularly after excessive doses, there has been an extreme reduction, even to 200 per cu. mm. The cases reported in this country have shown no clinical manifestations of agranulocytosis except fever. ApThomas and Cullumbine,<sup>4</sup> however, reported three cases of extreme depletion of all types of marrow cells following administration of the *tris* compound, in which stomatitis appeared. Presumably the administration of penicillin would reduce the risk of such infections.

The platelets are also reduced, usually to from 60,000 to 100,000 per cu. mm. In severe reactions they may be much more reduced, to 20,000 or less, and there may be a prolonged bleeding time, purpura and bleeding from the mucous membranes. There is a gradual recovery which about parallels that of the leukocytes. The red blood cells and hemoglobin as a rule are only slightly reduced (about 300,000 red cells and 1.0 gm. hemoglobin<sup>3</sup>), and there is a marked transient reduction in reticulocytes. ApThomas and Cullumbine,<sup>4</sup> however, observed one patient in whom the hemoglobin fell to 30 per cent. Recovery from such severe reactions is protracted, but no evidence of cumulative injury has been reported.

The most satisfactory clinical results have been obtained in Hodgkin's disease, of which 75 cases have been reported. Many of these were in an advanced stage of the disease and had become resistant to irradiation treatment. The number of early cases, previously untreated, was small. In most of the cases, nevertheless, there was at least temporary clinical improvement of significant degree, and this was not infrequently "dramatic," even in patients who were regarded as resistant to irradiation. In a few cases (3 of 27 cases of Jacobson et al.<sup>3</sup>), however, either no appreciable improvement was obtained or (in five others) it was quite transient. As a rule no basis for predicting an unfavorable result was evident.

In patients responding favorably there was prompt subjective improvement (in one to three days), with subsidence of fever and malaise, return

of appetite and increase in weight and strength. This was observed even in patients who appeared almost moribund. Some patients were able to return to work. Bone pain and particularly pruritus were less regularly relieved. With this subjective improvement there was rapid diminution in size (or disappearance) of the tumor masses and of the liver and spleen.

The remissions so obtained have been brief in most cases, on the average two to three months, exceptionally up to seven months. Relapses usually responded to a second course of treatment, and several patients have been maintained in good health for two to three years by repeated courses of treatment at intervals of two months or more as indicated by their clinical status. In three cases<sup>2</sup> sensitivity to irradiation was thought to have been restored by nitrogen mustard, and one patient obtained a remission after combined treatment although resistant to each procedure when used alone. In other cases the response to treatment was less satisfactory, remissions became shorter, and the patients eventually died of the disease. There is no evidence that any patient has been cured.

In lymphosarcoma the results reported were similar but less regularly obtained and not so well maintained. Of 21 cases reported, some improvement was observed in 13. Excellent results were obtained in some patients, even after they had become resistant to radiation,<sup>2</sup> and in several this was maintained for two years or more by repeated courses.<sup>2</sup>

In 12 cases of chronic leukemia reported by Goodman et al.<sup>2</sup> no improvement was obtained in six in an advanced stage of the disease. In six earlier cases the results were regarded as comparable to those following irradiation. Jacobson et al.<sup>3</sup> similarly obtained remissions in three of seven cases of chronic myeloid leukemia. In seven of eight cases of chronic lymphoid leukemia one or more remissions was obtained. Five of these patients died within about a year, however, and only two survived 18 to 21 months.

In five cases of polycythemia rubra<sup>3</sup> favorable results were obtained which may prove comparable to those following radio-active phosphorus.

In other diseases in which treatment with nitrogen mustards has been reported, little or no benefit has been obtained. These include nine cases of acute or subacute leukemia, two of multiple myeloma, one of follicular lymphoblastoma, and about 10 cases of other neoplasms of various types. The number of these cases is obviously too small to warrant any conclusions and further study is needed.

Only tentative conclusions can be drawn from the work thus far reported. It does suggest that the nitrogen mustards deserve a place, although probably a subsidiary one, in the treatment of Hodgkin's disease and lymphosarcoma and possibly in some cases of chronic leukemia. The manifest advantages the nitrogen mustards possess over radiation in the treatment of Hodgkin's disease are: Favorable results are obtained more promptly; the mustards are effective in some patients who have become resistant to irradiation and possibly may restore sensitiveness to irradiation in certain cases; the gastro-

intestinal disturbances caused by the treatment are usually less disturbing; and the treatment should be less expensive. It is possible, but not yet demonstrated, that if used as a supplement to radiation, they may increase its effectiveness. The remissions obtained, however, are usually much briefer, and injury to hemopoietic tissue is more severe and much more difficult to control. Neither procedure cures the disease but merely procures temporary remissions.

Many substances similar in chemical structure to these mustards are available or can be easily synthesized, and the hope is warranted that one may be found which is more effective and less toxic. Such a substance, however, would have to possess a remarkable degree of specificity in its action if it were to eliminate the lymphocytes in these neoplastic tissues without simultaneously injuring the normal lymphocytes and marrow cells.

Until much more experience has been gained, irradiation (as long as it is effective) remains the preferable treatment for general use.

P. W. C.

*The Medical Writings of Anonymous Londinensis.* By W. H. S. JONES, Litt.D., F.B.A. 168 pages; 22 × 14 cm. 1947. Cambridge University Press, New York. Price, \$2.75.

*Nursing.* By LULU K. WOLF, R.N., B.S., M.P.H., Professor of Nursing, Vanderbilt University School of Nursing. 534 pages; 22 × 15.5 cm. 1947. D. Appleton-Century Company, Incorporated, New York. Price, \$3.50.

*Recent Advances in Endocrinology* (Sixth Edition). By A. T. CAMERON, C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba, etc. 443 pages; 21 × 13.5 cm. 1947. The Blakiston Company, Philadelphia. Price, \$6.00.

*Specialties in Medical Practice* (loose leaf) (Renewal pages for Volume I and Volume II). EDGAR VAN NUYS ALLEN, M.D., Editor, Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, etc. With a Foreword by DONALD C. BALFOUR, M.D., F.A.C.S., F.R.C.S. (England), R.F.A.C.S., Consultant in Surgery, The Mayo Clinic, etc. 63 loose-leaf pages; 25 × 18 cm. 1947. Thomas Nelson & Sons, New York. Price, \$2.50 for renewal pages.

*Synopsis of Allergy* (Second Edition). By HARRY L. ALEXANDER, A.B., M.D., Professor of Clinical Medicine, Washington University School of Medicine, Saint Louis, etc. 255 pages; 20 × 13 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$3.50.

## COLLEGE NEWS NOTES

### THE AMERICAN COLLEGE OF PHYSICIANS' POSTGRADUATE COURSES

The Bulletin of Postgraduate Courses was published and distributed to members of the College during the month of July, giving adequate time for the arrangement of plans and the consummation of registrations. Physicians, however, were rather slow in registering during the summer months and the Committee on Postgraduate Courses believes that courses should not be scheduled in the future before the first of October, whereas this year, the first three courses, namely, Internal Medicine at the University of Pittsburgh, Psychosomatic Medicine at the University of Colorado, and Mechanics of Disease at the Peter Bent Brigham Hospital, Boston, were scheduled in early September but did not enjoy maximal registration as probably would have been the case had these courses been scheduled later in the autumn. As a matter of fact, the registration for the course in Psychosomatic Medicine was inadequate and the course was cancelled with deep regret, because of its excellence. An adequate, though not maximal, registration developed for Courses 1, 3 and 4. For Course 5, Physiological Basis of Internal Medicine, at the University of Pennsylvania Graduate School of Medicine under Dr. Julius Comroe, Jr., new on the College schedule, there was a phenomenal demand. The place of meeting was changed from the Medical Laboratories of the University of Pennsylvania to the large auditorium of the University Museum, and more than 150 physicians were in attendance.

#### Remaining Courses on Autumn Schedule

- No. 6—ADVANCED CARDIOLOGY  
Southwestern Medical College, Dallas  
Dr. Tinsley R. Harrison, Director  
November 3-8, 1947.
- No. 7—CHEMOTHERAPY—NEW DRUGS  
Boston University School of Medicine  
Dr. Chester S. Keefer, Director  
November 3-8, 1947.
- No. 8—INTERNAL MEDICINE  
University of Wisconsin Medical School, Madison  
Dr. William S. Middleton, Director  
November 3-14, 1947.
- No. 9—RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE  
Massachusetts General Hospital, Boston  
Dr. Paul D. White, Director  
November 10-22, 1947.
- No. 10—GASTRO-ENTEROLOGY  
Graduate Hospital of the University of Pennsylvania, Philadelphia  
Dr. Henry L. Bockus, Director  
November 17-26, 1947.
- No. 11—CARDIOVASCULAR DISEASE  
Yale University School of Medicine, New Haven  
Dr. H. M. Marvin, Director  
December 1-6, 1947.

## No. 12—GENERAL MEDICINE

University of Texas School of Medicine, Galveston

Dr. Charles T. Stone, Director

December 1-13, 1947.

Course 9 has been filled to capacity for many weeks.

These are all exceedingly fine courses, and accommodations are available at this time in all except Course 9.

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AUTUMN MEETING, BOARD OF REGENTS AND COMMITTEES

The regular autumn meeting of the Board of Regents and of the standing committees of the College will be held at the College Headquarters, Philadelphia, on Saturday and Sunday, November 22-23, 1947.

The Committee on Credentials will consider at this meeting only those candidates who were formally proposed and whose credentials were completely filed not later than September 23, 1947.

All matters requiring the attention of the Board of Regents should be submitted well in advance of November 21.

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HOTEL ACCOMMODATIONS, THE SAN FRANCISCO ANNUAL SESSION,  
APRIL 19-23, 1948

Many physicians are already desiring to make hotel reservations for the 29th Annual Session of The American College of Physicians at San Francisco. There are adequate hotel rooms available but there is no single hotel large enough to serve as the primary headquarters and to accommodate the bulk of the College members. Therefore, a group of "Official Hotels" has been selected and is herewith published. All hotels are reasonably convenient to the Civic Auditorium where meetings will be held.

It is obviously necessary that the College must be able to guarantee accommodations for the speakers on the program, distinguished guests, Officers, Regents and Governors. For this purpose the Fairmont and Mark Hopkins Hotels have been selected and no direct reservations are available there. The Executive Secretary of the College will make reservations for the above group, on request, at these hotels.

The Whitcomb Hotel has been assigned to the technical exhibitors, through the Medical Exhibitors Association. All technical exhibitors should apply for accommodations at the Whitcomb through the Medical Exhibitors Association.

Physicians, their families and friends may obtain accommodations at the following hotels by writing directly to the hotel, giving, specifically, the type of accommodation desired, the date of arrival, the date of departure and clearly identifying themselves with the College and this meeting. The absence of any quoted rates for single rooms indicates the hotel has guaranteed no single rooms. The various classes, A, B and C, in many instances indicate only comparisons in sizes, for many of the Class B hotels, though smaller, are comparable with the Class A hotels.

*"Official Hotels," San Francisco Meeting*

Class A Rating	Rates			
	Single	Double	Twin	Suites
<i>The Clift Hotel</i> Mr. Joseph Herlicy Geary & Taylor Sts.		\$7.00-9.00	\$8.00-12.00	\$20.00-30.00
<i>Palace Hotel</i> Mr. Edmond A. Rieder Market & New Montgomery Sts.		8.00-11.00	9.00-12.00	18.00-35.00
<i>St. Francis Hotel</i> Mr. Dan E. London Union Square		8.00-9.50	8.00-14.00	2-room units, with 1 bath, 18.00-20.00
<i>Sir Francis Drake Hotel</i> Mr. Clifford Shea 450 Powell St.	\$6.00-8.00	8.00-10.00	9.00-11.00	
Class B Rating				
<i>Bellevue Hotel</i> Mr. J. Paul Jones Geary at Taylor Sts.		6.00	6.50	10.00
<i>Californian Hotel</i> Mr. P. T. Loud 405 Taylor St.	3.00	5.25	6.00	12.00
<i>Canterbury Hotel</i> Mr. Howard M. Hall 750 Sutter St.		5.00-6.00	6.00-7.00	
<i>Chancellor Hotel</i> Mr. V. Jones 433 Powell St.		5.00	6.00	
<i>Drake-Wiltshire Hotel</i> Mr. Walter R. Bald 340 Stockton St.	2.50-3.00	4.00-5.00	6.00	
<i>Embassy Hotel</i> Mr. George Savy 610 Polk St.		4.00	4.00	
<i>Manx Hotel</i> Mr. George S. Schreiner 225 Powell St.	3.00-3.50	4.00-4.50	5.00-6.00	
<i>Maurice Hotel</i> Mr. Alex Hoffer 761 Post St.		5.00	6.00	10.00
<i>Stewart Hotel</i> Mr. Kenneth A. Stewart 351 Geary St.		4.00-4.50	4.50-5.00	2-room units, with 1 bath, 8.00



*"Official Hotels," San Francisco Meeting—Continued*

Class C Rating	Rates			
	Single	Double	Twin	Suites
<i>Barclay Hotel</i> Mr. Gabriel Bes 235 O'Farrell St.	2.50	3.00	3.50	
<i>Brayton Hotel</i> Mr. Ernest Louvau 50 Turk St.		3.50-4.00	5.00	2-room units, with 1 bath; 6.50-8.00
<i>Cartwright Hotel</i> Mr. Irving Edelman 524 Sutter St.		4.00	4.50	
<i>Columbia Hotel</i> Mr. Alan Strong 411 O'Farrell St. at Taylor		3.50	3.50	
<i>Commodore Hotel</i> Miss Tessie Turner 825 Sutter St.		Rates not quoted		
<i>Devonshire Hotel</i> Mr. Frank Benadom 335 Stockton St.	2.50	3.50-4.50	4.50-5.00	
<i>El Cortez Hotel</i> Mr. W. H. Sawtelle 550 Geary St.	3.50-5.00	4.50-6.00	6.00-7.00	
<i>Fielding Hotel</i> Mr. Ernest F. Peterson Geary at Mason Sts.		5.00	6.00	
<i>Keystone Hotel</i> Mr. Glen Gall 54 Fourth St.	3.00	3.50	5.00	
<i>Lankershim Hotel</i> Mr. S. D. Riddle 55 Fifth St.		3.50		
<i>Lombard Hotel</i> Miss Tessie Turner 1015 Geary St.		Rates not quoted		
<i>New Alden Hotel</i> Mr. J. A. Warren 333 Fulton St.		2.50-3.50		3-room units, with 1 bath, 4.00 4-room units, with 1 bath, 4.50
<i>Olympic Hotel</i> Mr. M. H. Lehr 230 Eddy St.		4.00-5.00	4.50-5.50	
<i>Pickwick Hotel</i> Mr. Joseph M. Lawrence 5th & Mission Sts.		4.00-5.00	4.50-5.50	

*"Official Hotels," San Francisco Meeting—Continued*

Class C Rating	Rates			
	Single	Double	Twin	Suites
<i>Powell Hotel</i> Mr. Loyal A. Hobson 17 Powell St.		4.00		3-room units, with 1 bath, 5.00 4-room units, with 1 bath, 6.00
<i>Roosevelt Hotel</i> Mr. Robert R. Vayssie 240 Jones St.	3.00-3.50	3.50-4.00		
<i>Senate Hotel</i> Mr. Hugo Jensen 467 Turk St.		3.00		3-room units, with 1 bath, 4.00 4-room units, with 1 bath, 5.00-6.00
<i>Senator Hotel</i> 519 Ellis St.		3.00	4.00	
<i>Shaw Hotel</i> Mr. C. J. Murphy Market & McAllister Sts.	3.50	5.00	6.00	
<i>Washington Hotel</i> Mr. D. Fitzgerald Grant Ave. & Bush St.		4.00-5.00	4.50-5.50	

## SPECIALTY BOARD ANNOUNCEMENTS

The American Board of Pediatrics, Inc., will hold oral examinations on December 5, 6, and 7, 1947, at Dallas, Tex.

The American Board of Radiology will hold an examination at the Statler Hotel, Boston, Mass., November 26-30, 1947.

The American Board of Psychiatry and Neurology, Inc., has tentatively scheduled regular examination in New York City, December 15, 16, and 17, 1947. Applications for admissions to this examination closed on September 15.

In order to avoid misunderstanding regarding the allowance of one year of training credit for work in the armed forces during wartime, it should be noted that wartime, to The American Board of Psychiatry and Neurology, Inc., means V-J Day plus six months. Therefore, men who entered the service on V-J Day would be allowed six months' credit. Those men who entered the armed forces after February of 1946 will not be granted credit toward the training requirements, unless they were residents in hospitals approved by this Board for residency training. If they have practiced psychiatry or neurology during this time, however, it is probable that this will be counted toward the experience requirements.

The Royal College of Physicians and Surgeons of Canada will hold oral and clinical examinations for the Diploma of Fellow, in Toronto, November 24-27, 1947.

From December 1 to 6, 1947, the American Trudeau Society will offer in San Francisco, for physicians in the states of California, Washington, Oregon, Idaho, and Nevada, a postgraduate course on diseases of the chest. Registration in this course will be limited to 30 internists interested in this field. The tuition fee will be Fifty Dollars. Information concerning registration and the program may be obtained from Cameron St. C. Guild, Executive Secretary, 1790 Broadway, New York 19, N. Y.

The course will be sponsored by the University of California Medical School, the Stanford University School of Medicine, and the San Francisco Department of Health. The Regional Sub-committee includes Dr. Carl R. Howson, F.A.C.P., Los Angeles; Dr. Sidney J. Shipman, F.A.C.P., San Francisco; and Dr. Harold G. Trimble, F.A.C.P., Oakland.

This is the third in a series of postgraduate courses presented by the Society. The most recent course was that given July 28-August 9 at Denver, Colo. The University of Colorado School of Medicine, Dr. Ward Darley, Jr., F.A.C.P., Dean, participated in this course, and the Regional Sub-committee included Dr. James J. Waring, F.A.C.P., Denver, as Chairman.

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The American Association for the Study of Goiter, of which Dr. J. H. Means, F.A.C.P., Boston, is President, will hold its annual session at Toronto, Canada, May 6-8, 1948. The Van Meter Prize Award of \$300, and two honorable mentions will then be made for the best essays on original work on thyroid problems. To be eligible, essays must be typed in English, double spaced, not more than 3,000 words, and submitted to Dr. T. C. Davison, Corresponding Secretary, 207 Doctors' Bldg., Atlanta 3, Ga., before February 1, 1948.

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The College takes pleasure in announcing that on August 20, 1947, Dr. Donald Maclean Willson, F.A.C.P., Milwaukee, Wis., became a Life Member of the College.

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Dr. Thomas Parran, F.A.C.P., Surgeon General of the United States Public Health Service, has been awarded the Typhus Commission Medal for his outstanding and inspiring contributions to the work of the Commission, both in the United States and overseas.

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Dr. Henry O. Colomb, F.A.C.P., New Orleans, has recently been appointed to the Professorship of Psychiatry in the Louisiana State University School of Medicine.

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Edwin P. Jordan, M.D., F.A.C.P., formerly of Chicago where he served as Associate Editor of the Journal of the American Medical Association and as a writer for the Chicago Sun Syndicate, has become Director of Medical Education and the Bunts Educational Institute of the Cleveland Clinic. In this new position Dr. Jordan will direct the institute's increased activities in postgraduate courses and fellowship training, as well as the lecture courses for practicing physicians.

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Colonel William D. Graham (MC), USA, F.A.C.P., has been appointed Chief of the Hospital Division in the Surgeon General's Office.

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Dr. James R. Reuling, F.A.C.P., Bayside, N. Y., has been elected President of the National Tuberculosis Association; Dr. Horton C. Hinshaw, F.A.C.P., Rochester, Minn., has been designated as President-Elect, and Dr. David A. Cooper, F.A.C.P., Philadelphia, Secretary-Treasurer.

Dr. John S. La Due, F.A.C.P., New York City, has been elected Secretary of the American Federation for Clinical Research.

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Dr. Walter L. Bierring, F.A.C.P., Commissioner, State Department of Health, Des Moines, Iowa, has contributed to the College Library of Publications by Members a copy of the new sixth edition of Rypins' "Medical Licensure Examinations," which has been prepared under his editorial direction and recently published by J. B. Lippincott Company, Philadelphia.

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Dr. John M. Swan, Rochester, N. Y., has donated to the American College of Physicians Library a copy of the "Transactions of the John Guiteras Medical Society of Undergraduates of the University of Pennsylvania," for the year 1892-93. Dr. Swan was the President of that Society during his third year in the Medical School of the University of Pennsylvania, and this publication is a worthy example of the work of the undergraduate group under the inspiration of a great leader of his day.

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#### NEUROLOGISTS AND PSYCHIATRISTS IN THE AMERICAN COLLEGE OF PHYSICIANS

A recent survey of the membership of the American College of Physicians reveals that there are 67 Associates and 215 Fellows, or a total of 285, who give neurology, psychiatry, or neuropsychiatry as their primary specialties. There is an almost equal number who give one of these specialties as their secondary field of interest.

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#### THE CHIEF MEDICAL DIRECTOR OF THE VETERANS ADMINISTRATION REPORTS

Dr. Paul R. Hawley, F.A.C.P., Chief Medical Director of the Veterans Administration, who has recently been made an Honorary Fellow of the American Association for the Surgery of Trauma, in a report to the Branch Medical Directors, Managers of Hospitals and Centers, Managers of Regional Offices, and Veterans Administration Offices having Medical Divisions, on September 2, 1947, reported, in part, as follows: "While much still remains to be done, we may well be gratified with our achievements during this past year. Quantitative measurements cannot begin to tell the story, for our greatest accomplishment has been the marked progress towards our goal of providing all eligible beneficiaries with the best possible medical service in accordance with the highest current professional standards. The human suffering that has been avoided by more rapid and more effective therapy, the achievements of the mental hygiene program in staving off mental illness, and of the medical rehabilitation program in rebuilding shattered lives, the changing emphasis in neuropsychiatric hospitals from custodial care to genuine treatment, and many other equally significant advances—none of these can be calculated in cold statistical terms.

"However, even when judged by quantitative standards alone, our achievements during the past fiscal year have been impressive. A total of 386,614 veterans were admitted to our hospitals during the Fiscal Year 1947, compared to 271,299 for the previous year. VA patients hospitalized during the year at any one time averaged 98,600, compared to 78,900 during the previous year, an increase of 25 per cent. Our hospital plant had 108,225 authorized beds and 101,273 available beds as of June 30, 1947, compared to 91,675 authorized and 87,369 available beds as of June 30, 1946. A total of 2,744,602 individuals were given medical examinations and 564,171 individuals were given dental examinations during Fiscal Year 1947, a marked increase over the comparable figures of 1,036,634 individuals examined medically and 85,537 individuals given dental examinations during the preceding year. A similar growth was manifested in medical and dental out-patient treatments."

## AMERICAN ACADEMY OF GENERAL PRACTICE

At the 1947 Atlantic City Convention of the American Medical Association, the American Academy of General Practice was founded. The purposes of this new organization, as stated in the constitution, are to promote and maintain high standards in the general practice of medicine and surgery; to encourage study for general practitioners; to encourage young people to qualify for general practice; to maintain and enhance the prestige of general practice; and to advance medical science and health. This organization is not of the nature of a certifying or accrediting board. Dr. Paul A. Davis, Akron, Ohio, has been elected first President of the Academy. Initiation fee is \$10.00 and dues are \$15.00 per year.

## PROGRAMS OF RECENT REGIONAL MEETINGS

At the time of writing, a number of Regional Meetings of the College have been held for which information concerning registration has not yet been received. Accordingly, the programs of these meetings are here presented in summarized form without comments.

*Western Pennsylvania*

This meeting was held at Pittsburgh on Wednesday, September 10, under the Governorship of R. R. Snowden, M.D., F.A.C.P. The morning program consisted of a symposium on diseases of the liver in which Campbell Moses, M.D. (by invitation), spoke on "The Physiology of the Diseased Liver"; John F. Beauregard, M.D. (by invitation), on "Infectious Hepatitis"; and Morris Hersenson, M.D., F.A.C.P., on "The Clinical Use of Liver Function Tests." These speakers were all from the University of Pittsburgh School of Medicine. The afternoon session took place at the Buhl Planetarium and Hall of Science and included a demonstration of the planetarium projector by Arthur L. Draper, Ph.D., Director of the Planetarium, and a demonstration and an exhibit on nuclear physics and nuclear energy. Cocktails and a banquet at the Pittsburgh Athletic Association Annex were followed by a musical program and brief talks by distinguished guests, among whom were listed Dr. Walter W. Palmer, New York City, President-Elect of the College; Dr. A. B. Brower, Dayton, Ohio, Regent of the College; and Dr. M. A. Blankenhorn and Dr. D. A. MacGregor, College Governors for Ohio and West Virginia, respectively.

*Oklahoma*

On Saturday, September 20, 1947, this meeting was held at Oklahoma City, Wann Langston, M.D., F.A.C.P., Governor, acting as General Chairman. The following papers were presented by Fellows of the College in the Morning Session at the University of Oklahoma Medical School Building: "Gaseous Exchange and Fluid Mobilization," by Edward C. Mason, Oklahoma City; "The Use of Diuretics," by John B. Morey, Ada; "Cerebral Manifestations of Digitalis Intoxication," by Russell C. Pigford, Tulsa; "Adreno-Cortical Syndromes," by Henry C. Turner, Oklahoma City. Also included in the Morning Session were a clinic—"Peripheral Vascular Disease"—by George N. Barry, M.D., F.A.C.P., and John Powers Wolff, M.D. (by invitation), both of Oklahoma City, and a panel discussion on Chemotherapy, of which Dr. Langston was moderator and in which the following subjects were discussed by Fellows from Oklahoma City: "Sulphonamides," by R. Q. Goodwin; "Penicillin in Infections Other than Syphilis," by W. W. Rucks, Jr.; "Streptomycin in Tuberculosis," by Floyd Moorman. Phyllis Jones, M.D. (by invitation), Oklahoma City, and E. Rankin Denny, M.D., F.A.C.P., Tulsa, also participated in the discussion, their sub-

jects being "Penicillin in Syphilis" and "Streptomycin in Infections Other than Syphilis," respectively. Luncheon was served at the University Hospital. The Afternoon Session included a talk by Dr. Hugh J. Morgan, President of the College, and the following papers: "Some Problems in Nutrition," by Paul B. Cameron, M.D. (Associate), Prior; "Infectious Hepatitis," by Charles J. Roberts, M.D. (Associate), Enid; "The Present-Day Management of Peptic Ulcer," by Harry A. Daniels, M.D., F.A.C.P., Oklahoma City; "X-Ray Diagnosis of Peptic Ulcer," by John R. Danstrom, M.D. (by invitation), Oklahoma City. Following this there was a clinical pathological conference by Emil J. Palik, M.D. (by invitation), Tulsa. Open discussion was invited. At the dinner in the evening at the Hotel Biltmore, Dr. Wann Langston was Toastmaster and Dr. Hugh J. Morgan was Guest Speaker.

### *Nebraska*

The Nebraska Regional Meeting took place at the Cornhusker Hotel, Lincoln, Saturday, September 20, 1947, under the Governorship of Joseph D. McCarthy, M.D., F.A.C.P., of Omaha, and with George W. Covey, M.D., F.A.C.P., acting as Chairman of the Program Committee. The following papers were presented: "Calcium, Phosphorus, and Serum Determinations as Observed at the University of Nebraska Hospital," by Esley J. Kirk, M.D., F.A.C.P., Omaha; "Treatment of Subacute Bacterial Endocarditis," by Arthur L. Smith, Jr., M.D. (Associate), Lincoln; "Spontaneous Hemopneumothorax," by W. Wayne Waddell, M.D. (Associate), Beatrice; "Arthritis in Amoebiasis," by Horace H. Zinneman, M.D. (Associate), Lincoln; "Thiouracil in the Treatment of Hypertensive Cardiovascular Disease," by Benjamin F. Wolverton, M.D., F.A.C.P., Cedar Rapids, Iowa; and "The Use and Abuse of Irradiation Therapy in the Treatment of Uterine Bleeding," by J. Marshall Neely, M.D., F.A.C.P., Lincoln. An open discussion followed. Cocktails were served in the evening. At the dinner, Dr. Joseph D. McCarthy presided, Benjamin F. Wolverton, M.D., F.A.C.P., Governor for Iowa, spoke on "Current Problems of The American College of Physicians," and R. G. Gustavson, Ph.D., Chancellor, University of Nebraska, Lincoln, talked on "The Newer Chemistry in Medicine."

### *Iowa*

The Des Moines Club was the locus of this meeting on Saturday, September 27, 1947. The meeting was under the Governorship of B. F. Wolverton, M.D., F.A.C.P., Cedar Rapids, with George E. Mountain, M.D., F.A.C.P., Des Moines, as Chairman of the Program Committee. The program consisted of an informal luncheon and an afternoon session at which the following papers were presented by Iowa physicians: "The Prothrombin Time in Dicumarol Therapy," by Francis C. Coleman (by invitation), Des Moines; "Review of Nitrogen Mustard Therapy," by Willis M. Fowler, F.A.C.P., Iowa City; "Paroxysmal Cardiac Dyspnea," by Hyman M. Hurevitz (Associate), Davenport; "Management of Tuberculosis by the Internist," by Leon J. Galinsky (Associate), Des Moines; "The Precordial Electrocardiogram," by Lewis E. January (Associate), Iowa City; "Polyneuritis Due to Hematoporphyria," by Adolph L. Sahs, F.A.C.P., Iowa City; "Electroshock Treatments," by Frank J. Piekenbrock (Associate), Dubuque. Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., was Guest Speaker, his paper being entitled, "Clinical and Psychological Consideration of Patients with Cirrhosis." Dinner was preceded by cocktails. Herman J. Smith, M.D. (Associate), Des Moines, presided for the evening session at which Walter L. Bierring, M.D., F.A.C.P., Des Moines, spoke on "The American College of Physicians in Retrospect and in Prospect." and a motion picture on Cardiology was shown.

*New England*

A fine program was arranged by Dr. E. L. Amidon, Governor for Vermont, for members of the College in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont, at Burlington, Vt., on October 14. College members in the Province of Quebec and the Maritime Provinces also were invited.

W. E. Brown, M.D., Dean of The College of Medicine of the University of Vermont, welcomed the group to the University's Fleming Museum. Papers were presented by Harris B. Shumacker, Jr., M.D. (by invitation), New Haven, on "Sympathetic Nerve Surgery: Its Usefulness and Limitations"; by Charles H. Burnett, M.D. (by invitation), Boston, on "Kidney Physiology"; by Jarrett H. Folley, M.D. (Associate), Hanover, on "Aplastic Anemia"; by I. M. Rabinowitch, M.D., F.A.C.P., Montreal, on "Relationship between Liver Function and Premature Development of Arteriosclerosis in Diabetes Mellitus"; by Walter C. Lobitz, Jr., M.D. (by invitation), Hanover, on "The Skin and Lymphoblastoma"; by James W. Culbertson, M.D. (by invitation), Boston, on "Hypertension"; by Alex. M. Burgess, F.A.C.P., Providence, on "Excessive Hypertension of Long Duration"; and by Robert D. Roach, M.D., F.A.C.P., on "Pericarditis."

The scientific session was followed by a dinner at the Ethan Allen Club, at which C. H. Beecher, M.D., F.A.C.P., Burlington, presided. The guest address was by Mr. A. E. Whiting, General Manager of *The Herald*, Montreal. The list of distinguished guests included Dr. Walter W. Palmer, New York, Dr. Reginald Fitz, Boston, Dr. Francis G. Blake, New Haven, President-Elect, First and Second Vice Presidents of the College, respectively, as well as A.C.P. Regents Charles F. Moffatt, M.D., C.M., Montreal, and Alex. M. Burgess, M.D., Providence.

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PHILADELPHIA DEPARTMENT OF PUBLIC HEALTH OFFERS OPENING FOR ASSISTANT  
DIRECTOR, MEDICAL EDUCATION

Dr. P. F. Lucchesi, Superintendent and Medical Director of the Philadelphia General Hospital, in conjunction with the Philadelphia Department of Public Health, announces an opening for an Assistant Director of Medical Education, Grade 12, \$4,200-\$4,800 a year and maintenance. Candidates should file applications immediately to Dr. Lucchesi at the Philadelphia General Hospital, 34th St. and Curie Ave., Philadelphia 4, Pa.

Duties: Under the direction of the Superintendent and Medical Director, to have administrative charge of, and be responsible for, the direction, assignment, instruction, training and scheduling of the work and training program for resident physicians, internes and medical and postgraduate students assigned to the hospital; to confer and advise with staff members concerning the examination, activities and performance records of this group; to prepare teaching schedules and material for lectures; to be responsible for the development of the medical education program; to make recommendations for changes and improvements in the rules, regulations, technics and procedures of the hospital; to plan, prepare and edit reports and scientific papers issued or published by the hospital; to be responsible for the handling of public relations and the preparation of reports for newspapers, periodicals and medical journals; etc.

Training and experience count four points in the qualifications; practical questions, four points; and personal interview, two points.

Minimum requirements include: An M.D. degree from an acceptable medical school; license to practice medicine in Pennsylvania; two years of experience as assistant to a Medical Director and one year of experience in a hospital administra-

tive division; thorough knowledge of the fundamental sciences underlying the practice of medicine in its various branches; thorough knowledge of the examination, diagnosis and treatment of medical and surgical cases; some experience in hospital and medical publicity work; supervisory and administrative ability; ability to plan and prepare teaching programs; editorial ability in medical publication; public speaking ability on medical educational matters; ability to meet with the public; thoroughness; tact; high moral standards; good physical condition.

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#### NEW RESEARCH DIRECTOR

##### SMITH, KLINE & FRENCH LABORATORIES

Smith, Kline & French Laboratories, Philadelphia, Pa., have announced the appointment, as Director of their Research Laboratories, of Maurice L. Moore, B.S., University of Florida, 1930; Ph.D., Northwestern University, 1934. Dr. Moore has been Assistant Director of Research of Frederick Stearns and Company. Retiring Chairman of the Division of Medicinal Chemistry of the American Chemical Society, Dr. Moore also is a Fellow of the American Association for the Advancement of Science and a member of the American Institute of Chemists, American Pharmaceutical Association, Society of Chemical Industry, and the Pennsylvania Academy of Science. Active in the study of sympathomimetic amines, a field of interest to Smith, Kline & French for the past fifteen years, Dr. Moore has also made important discoveries in the course of studies of sulfonamides which he began some years ago as a Research Fellow in organic chemistry at Yale University.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to September 12, 1947 inclusive).

Elizabeth Brakeley, Montclair, N. J. (Major, USPHS(R))  
Sidney Miller, Rochester, Minn. (Major, MC, AUS)  
Joseph G. Rushton, Rochester, Minn. (Capt., MC, AUS)

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#### A.C.P. POSTGRADUATE COURSES STILL OPEN FOR REGISTRATION

There remain facilities to accommodate all interested members and some qualified non-members in Course No. 10, Gastro-enterology, and in Course No. 12, General Medicine, at the Graduate Hospital of the University of Pennsylvania and the University of Texas School of Medicine, respectively. To acquaint all interested physicians with the full details of these courses, a full outline is herewith published. It is recommended, however, that anyone wishing to register communicate immediately with

E. R. Loveland, Executive Secretary  
The American College of Physicians  
4200 Pine Street  
Philadelphia 4, Pa.



## COURSE No. 10—GASTRO-ENTEROLOGY

*(November 17-26, 1947)**Graduate Hospital of the University of Pennsylvania and the Philadelphia General Hospital, Philadelphia, Pa.*HENRY L. BOCKUS, M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 75)

Fee: A.C.P. Members, \$45.00. Non-Members, \$90.00

*Officers of Instruction*

Thomas P. Almy, M.D., Assistant Professor of Medicine, Cornell University College of Medicine, New York, N. Y.

William Bates, M.D., F.A.C.S., Professor of, and Vice Dean for, Surgery, University of Pennsylvania Graduate School of Medicine.

Joseph T. Beardwood, Jr., M.D., F.A.C.P., Professor of Diseases of Metabolism, University of Pennsylvania Graduate School of Medicine.

Lawrence H. Beizer, M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania Graduate School of Medicine.

Samuel Bellet, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

J. Edward Berk, M.D., F.A.C.P., Assistant Professor of Medicine, Temple University School of Medicine.

Henry L. Bockus, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Julius H. Comroe, Jr., M.D., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine.

George Eaton Daniels, M.D., Clinical Professor of Psychiatry, Columbia University College of Physicians and Surgeons, New York, N. Y.

David L. Drabkin, M.D., Professor of Physiological Chemistry, University of Pennsylvania Graduate School of Medicine.

William E. Ehrich, M.D., Professor of Pathology, University of Pennsylvania Graduate School of Medicine.

L. Kraeer Ferguson, M.D., F.A.C.S., Professor of Surgery, University of Pennsylvania Graduate School of Medicine.

Arthur Finkelstein, M.D., Assistant Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

Herbert S. Gaskill, M.D., Associate in Psychiatry and in Medicine, University of Pennsylvania School of Medicine.

W. Paul Havens, Jr., M.D., Associate Professor of Preventive Medicine and Associate in Medicine, Jefferson Medical College.

Herbert R. Hawthorne, M.D., F.A.C.S., Professor of Clinical Surgery, University of Pennsylvania Graduate School of Medicine.

J. Warren Hundley, Jr., M.D., F.A.C.P., Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Thomas A. Johnson, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

George P. Keefer, M.D., Instructor in Radiology, University of Pennsylvania Graduate School of Medicine.

Mack Lopusniak, M.D., Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

- Balduin Lucké, M.D., Professor of Pathology, University of Pennsylvania School of Medicine.
- Thomas E. Machella, M.D., Assistant Professor of Medicine and Instructor in Physiology, University of Pennsylvania School of Medicine.
- Thomas M. McMillan, M.D., F.A.C.P., Associate Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.
- Merle M. Miller, M.D., F.A.C.P., Assistant Professor of Allergy, University of Pennsylvania Graduate School of Medicine.
- T. Grier Miller, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine.
- James F. Monaghan, M.D., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- John R. Neefe, M.D., Associate in Medicine, University of Pennsylvania School of Medicine.
- Wilbur W. Oaks, M.D., Associate in Surgery, University of Pennsylvania Graduate School of Medicine.
- Johannes F. Pessel, M.D., F.A.C.P., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Edward C. Raffensperger, M.D., Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Abraham E. Rakoff, M.D., Associate in Gynecology and Obstetrics, Jefferson Medical College; Endocrinologist, Department of Clinical Laboratories, Jefferson Medical College Hospital.
- I. S. Ravdin, M.D., F.A.C.S., John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.
- Joseph A. Ritter, M.D., Associate Professor of Pediatrics, University of Pennsylvania Graduate School of Medicine.
- Maurice M. Rothman, M.D., Associate in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Alexander Rush, M.D., Assistant Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Thomas S. Sappington, M.D., American College of Physicians Fellow in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Harry Shay, M.D., Clinical Professor of Medicine, Temple University School of Medicine.
- Calvin M. Smyth, Jr., M.D., F.A.C.S., Professor of Clinical Surgery, University of Pennsylvania Graduate School of Medicine.
- J. Earl Thomas, M.D., Professor of Physiology, Jefferson Medical College.
- Gabriel Tucker, M.D., F.A.C.S., Professor of Bronchology, Esophagology and Laryngeal Surgery, University of Pennsylvania Graduate School of Medicine.
- Henry J. Tumen, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Edward Weiss, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.
- Bernard B. Widmann, M.D., Professor of, and Vice Dean for, Radiology, University of Pennsylvania Graduate School of Medicine.
- John H. Willard, M.D., F.A.C.P., Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.
- Stewart G. Wolf, Jr., M.D., Assistant Professor of Medicine, Cornell University Medical College, New York, N. Y.
- Joseph C. Yaskin, M.D., Professor of Neurology, University of Pennsylvania Graduate School of Medicine.

Harold A. Zintel, M.D., Assistant Instructor in Surgery, University of Pennsylvania School of Medicine.

David E. Zion, M.D., Instructor in Radiology, University of Pennsylvania Graduate School of Medicine.

The course is designed to give a survey of recent developments in gastroenterology. Considerable emphasis is placed on gastrointestinal physiology. The program comprises didactic presentations, conferences, case presentations and panel discussions. The teachers have been selected with care, including members of the faculty of several nearby medical schools in addition to those of the faculty of the University of Pennsylvania.

This course is scheduled for one and one-half weeks and will be concluded at noon, November 26, the day before Thanksgiving. Certain sessions will be held in the North Lecture Room of the Graduate Hospital of the University of Pennsylvania, 19th and Lombard Sts., and other sessions will be held in the auditorium of the Administration Building of the Philadelphia General Hospital, 34th St. below Spruce.

A special feature of the course will be the Eastern Pennsylvania Regional Meeting of the College on Friday afternoon, November 21, including luncheon at the College Headquarters and a scientific program, reception and dinner at the Warwick Hotel in the afternoon and evening. All members of the class are cordially invited. Dr. Hugh J. Morgan, President of the College, several members of the Board of Regents and other distinguished guests will be in attendance.

*Hotel Accommodations:* The Warwick Hotel, 17th and Locust Sts., Philadelphia 3, will accommodate registrants, provided that in making application they identify themselves with the College and this course. However, unless conditions change in the meantime, it will be necessary that members share large, twin-bedded rooms, due to the dearth of single rooms. Rates: Double, twin-bedded rooms, \$8, \$9 and \$10.

### *Outline of Course*

#### *Monday, November 17.*

A.M. Session—Philadelphia General Hospital—Auditorium, Administration Building.

8:15–9:00 Registration.

9:00–9:10 Assembly and Introductory Remarks.

Dr. R. C. Buerki, Dean, University of Pennsylvania Graduate School of Medicine, and Dr. Bockus.

9:10–9:30 Pyrosis: Its Mechanism and Clinical Significance.

Dr. Tumen.

### DIFFERENTIAL DIAGNOSIS OF ANGINA PECTORIS

9:30–9:45 Mechanism of Anginoid Pain.

Dr. Comroe.

9:45–10:00 Is It True Angina Pectoris?

Dr. McMillan.

10:00–10:15 Anginoid Pain Due to Alimentary Tract Disorders.

Dr. Bockus.

10:15–10:45 Esophagoscopy in Diagnosis and Treatment of Esophageal Lesions.

Dr. Tucker.

10:45–10:55 Intermission.

10:55–11:10 Roentgen Demonstration of Esophageal Lesions and Hiatal Hernia.

Dr. Zion.

11:10–11:20 Mechanism of Development of Cardiospasm and Functional Mega-esophagus.

Dr. Machella.

- 11:20-11:35 Diagnosis and Medical Treatment of Cardiospasm and Functional Mega-esophagus.  
Dr. Willard.
- 11:35-11:45 Surgical Treatment of Functional Mega-esophagus.  
Dr. Hawthorne.
- 11:45-12:00 Diagnosis and Medical Treatment of Hiatus Hernia.  
Dr. Johnson.
- 12:00-12:10 Operation for Hiatus Hernia.  
Dr. Ferguson.

#### CARCINOMA OF THORACIC ESOPHAGUS AND CARDIA

- 12:10-12:30 Clinical Aspects.  
Dr. Monaghan.
- 12:30-12:45 Surgical Approach.  
Dr. Hawthorne.
- P.M. Session—The Graduate Hospital.
- 2:15- 3:00 Remarks on Mechanism of Abdominal Pain.  
Dr. Bockus.
- 3:00- 3:30 Functions of the Stomach as Observed in Fistulous Human Subjects.  
Dr. Wolf.
- 3:30- 4:00 Value of Certain Gastric Analysis Procedures (Histamine, Caffeine and Insulin Tests).  
Dr. Berk.
- 4:00- 4:10 Intermission.
- 4:10- 5:20 Presentation of Patients, Illustrating Current Problems in Diagnosis and Therapy.  
Dr. Bockus and Colleagues.

#### *Tuesday, November 18.*

##### A.M. Session—Philadelphia General Hospital.

- 9:00- 9:30 Gastroscopy and X-Ray in the Diagnosis of Chronic Gastritis.  
Drs. Monaghan and Finkelstein.
- 9:30-10:00 Incidence and Clinical Importance of Achlorhydria.  
Dr. Johnson.
- 10:00-10:20 Mechanism of Secretory and Motor Behavior of Stomach in Duodenal Ulcer Disease.  
Dr. Shay.
- 10:20-10:40 The Personality Pattern and the Role of Emotional Tension in the Patient with Duodenal Ulcer.  
Dr. Gaskill.
- 10:40-11:00 Etiology and Pathogenesis of Duodenal Ulcer.  
Dr. Tumen.
- 11:00-11:10 Intermission.

#### DIAGNOSIS OF DUODENAL ULCER

- 11:10-11:30 Clinical Aspects.  
Dr. Shay.
- 11:30-11:45 X-Ray.  
Dr. Finkelstein.

#### THERAPY OF UNCOMPLICATED DUODENAL ULCER

- 11:45-12:15 Principles of Therapy in Healing of Active Ulcer.  
Dr. Willard.

- 12:15-12:30 Future of Hormones in Ulcer Therapy.  
Dr. Shay.
- 12:30-12:40 Place of Protein Hydrolysates.  
Dr. Sappington.
- 12:40- 1:00 Cause and Prevention of Recurrences.  
Dr. Johnson.
- P.M. Session—Philadelphia General Hospital.

STATUS OF INTERRUPTION OF VAGUS FIBERS IN PEPTIC ULCER THERAPY  
(Panel Discussion)

- 2:15- 2:30 Physiologic Basis.  
Dr. Comroe.
- 2:30- 2:40 Possible Indications.  
Dr. Bockus.
- 2:40- 2:50 Is Complete Vagotomy Easy of Accomplishment?  
Dr. Hawthorne.
- 2:50- 3:00 Methods of Determining Efficiency of Operation.  
Dr. Berk.
- 3:00- 3:15 Results: Healing of Ulcer and Recurrences.  
Dr. Tumen.
- 3:15- 3:25 Undesirable Side Effects and Their Management.  
Dr. Machella.
- 3:25- 3:40 Questions and Answers.
- 3:40- 4:00 Intermission.

DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT GASTRIC ULCER

- 4:00- 4:15 The Pathologist's Viewpoint.  
Dr. Ehrlich.
- 4:15- 4:45 Complementary Value of Gastroscopy and X-Ray.  
Drs. Monaghan and Finkelstein.

MANAGEMENT OF GASTRIC ULCER

- 4:45- 5:00 The Clinician's Viewpoint.  
Dr. Bockus.
- 5:00- 5:15 The Surgeon's Viewpoint.  
Dr. Smyth.

*Wednesday, November 19.*

A.M. Session—Philadelphia General Hospital.

- 9:00- 9:15 Indications for Subtotal Gastrectomy in Peptic Ulcer.  
Dr. Johnson.
- 9:15- 9:30 Surgical Principles Involved and Results of Subtotal Gastrectomy.  
Dr. Ferguson.

PEPTIC ULCER AND PYLORIC OBSTRUCTION

- 9:30- 9:50 Manner of Development of Hypochloremia, Alkalosis and Hyperazotemia.  
Dr. Drabkin.
- 9:50-10:05 Therapeutic Regimen and Decision for or against Operation.  
Dr. Willard.

## MASSIVE BLEEDING FROM UPPER GASTROINTESTINAL TRACT

- 10:05-10:30 Outline of Initial Therapy, Emphasizing Differential Diagnosis.  
Dr. Tumen.
- 10:30-10:40 Mechanism of Development of Hyperazotemia and Its Prognosis.  
Dr. Bockus.
- 10:40-10:50 Dietary Management of Bleeding Peptic Ulcer.  
Dr. Johnson.
- 10:50-11:00 When to Operate.  
Dr. Monaghan.
- 11:00-11:10 Intermission.
- 11:10-11:30 Remarks on Non-operative Treatment of Perforated Peptic Ulcer.  
Dr. Bockus.
- 11:30-11:50 Surgery of Perforated Ulcer: Results.  
Dr. Ravdin.
- 11:50-12:10 Diagnosis and Management of Gastrojejunal Ulcer.  
Dr. T. Grier Miller.
- 12:10-12:30 Gastrojejunal Colic Fistula.  
Dr. Johnson.
- 12:30-12:50 Repair of Gastrojejunicolic Fistula: Case Presentation.  
Dr. Ferguson.
- P.M. Session—The Graduate Hospital.
- 2:30- 3:00 Differential Diagnosis of Constricting Lesions of the Pylorus: Case  
Presentations.  
Dr. Berk.
- 3:00- 3:30 Present Status of Gastric Syphilis.  
Dr. Monaghan.
- 3:30- 4:00 Intramural Gastric Tumors.  
Dr. Bockus.
- 4:00- 4:10 Intermission.
- 4:10- 5:30 Presentation of Patients Illustrating Current Problems in Diagnosis  
and Therapy.  
Dr. Bockus and Colleagues.

*Thursday, November 20.*

A.M. Session—Philadelphia General Hospital.

- 9:00- 9:20 Prognosis of Gastric Carcinoma.  
Dr. Berk.
- 9:20-9:40 The Clinical Importance of Duodenal Diverticulitis.  
Dr. Johnson.
- 9:40- 9:55 Surgical Management of Duodenal Diverticulosis.  
Dr. Ferguson.
- 9:55-10:15 Postbulbar Duodenal Ulcer.  
Drs. Monaghan and Finkelstein.

## FUNCTIONS OF THE LIVER

- 10:15-10:45 Formation and Excretion of Bile.  
Dr. Tumen.
- 10:45-10:55 Intermission.
- 10:55-11:25 Role of the Liver in the Metabolism of Carbohydrate, Protein and Fat.  
Dr. Drabkin.
- 11:25-11:40 Aspiration Liver Biopsy.  
Dr. Oaks.

- 11:40-11:55 Peritoneoscopy.  
Dr. Oaks.
- 11:55-12:10 X-Ray Study of the Liver: Thorotrast.  
Dr. Finkelstein.
- 12:10-12:20 Esophageal Varices.  
Dr. Zion.
- 12:20-12:50 Differential Diagnosis of Jaundice.  
Dr. Shay.
- P.M. Session—The Graduate Hospital.
- 2:15- 3:30 Gastrointestinal Conference.  
Staff.
- 3:30- 3:40 Intermission.

#### VIRUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE

- 3:40- 4:10 Epidemiological and Clinical Features.  
Dr. Havens.
- 4:10- 4:35 Pathology.  
Dr. Lucké.
- 4:35- 5:00 Value of Liver Function Tests in Diagnosis and Prognosis.  
Dr. Neeffe.
- 5:00- 5:20 Treatment.  
Dr. Berk.

*Friday, November 21.*

A.M. Session—Philadelphia General Hospital.

#### HEPATIC CIRRHOSIS

- 9:00- 9:20 Present Concept of Etiology of Cirrhosis.  
Dr. Monaghan.
- 9:20- 9:30 Pathology of Hepatic Cirrhosis.  
Dr. Ehrlich.
- 9:30-10:00 Value of Liver Function Tests in Diagnosis and Prognosis.  
Dr. Tumen.
- 10:00-10:15 The Sex Hormones in Cirrhosis of the Liver.  
Dr. Rakoff.
- 10:15-10:30 Control of Ascites and Hemorrhage in Cirrhosis.  
Dr. Bockus.
- 10:30-10:45 Factors Influencing Prognosis in Hepatic Cirrhosis.  
Dr. Willard.
- 10:45-11:00 Hemochromatosis.  
Dr. Berk.
- 11:00-11:10 Intermission.
- 11:10-11:25 Technical Aspects and Interpretation of Cholecystography in Gall-  
bladder Disease.  
Dr. Finkelstein.
- 11:25-11:45 Indications for and Interpretation of Diagnostic Biliary Drainage in  
Biliary Tract Disease.  
Dr. Willard.
- 11:45-12:10 Diagnosis and Management of Acute Cholecystitis.  
Dr. Berk.
- 12:10-12:40 Pre- and Postoperative Care of the Jaundiced Patient.  
Dr. Ravdin.

12:40-12:55 Postoperative Cholangiography.  
Dr. Zion.

P.M. Session.

### EASTERN PENNSYLVANIA REGIONAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

1:00 Buffet Luncheon.

College Headquarters, 4200 Pine Street.

3:00 Scientific Program, Ballroom, Warwick Hotel, 17th & Locust Streets.

(This program, being prepared by Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, will be published in special pamphlet form, and distributed in advance to all members of the class. All are cordially invited to participate in the entire Regional Meeting.)

6:30 Reception and Cocktails, Warwick Hotel.

7:15 Dinner.

Many distinguished guests, including the President of the College, Dr. Hugh J. Morgan, will be in attendance. Music and entertainment by a well known quartette.

*Saturday, November 22.*

A.M. Session—Philadelphia General Hospital.

### SYMPOSIUM ON THE PANCREAS

9:00- 9:30 Physiology of the Pancreas.

Dr. Thomas.

### TESTS FOR PANCREATIC FUNCTION

9:30- 9:45 Duodenal Intubation.

Dr. Lopusniak.

9:45-10:05 Pancreatic Serum Enzymes.

Dr. Johnson.

10:05-10:20 Chemical Analysis of Feces.

Dr. Sappington.

10:20-10:35 Microscopic Analysis of Feces.

Dr. Rothman.

10:35-10:45 Intermission.

10:45-11:05 Diagnosis and Treatment of Acute Pancreatitis.

Dr. Bockus.

11:05-11:15 Electrocardiographic Changes in Acute Pancreatitis.

Dr. Bellet

11:15-11:30 Analysis of Recent Graduate Hospital Cases of Acute Pancreatitis.

Dr. Raffensperger.

11:30-11:45 Cystic Fibrosis of Pancreas.

Dr. Ritter.

11:45-12:00 Islet Cell Tumors of the Pancreas.

Dr. Beardwood.

12:00-12:25 Diagnosis of Carcinoma of Pancreas.

Dr. Berk.

12:25-12:40 X-Ray Diagnosis of Pancreatic Carcinoma.

Dr. Finkelstein.

12:40- 1:00 Surgical Treatment of Carcinoma of Pancreas.

Dr. Ferguson.



*Monday, November 24.*

A.M. Session—Philadelphia General Hospital.

RECOGNITION AND CARE OF NUTRITIONAL DEFICIENCIES IN GASTROINTESTINAL  
DISORDERS

- 9:00–9:20 Protein Deficiency.  
Dr. Sappington.
- 9:20–9:40 Anemia.  
Dr. Beizer.
- 9:40–10:00 Avitaminosis.  
Dr. Monaghan.
- 10:00–10:15 Steatorrhea.  
Dr. Bockus.
- 10:15–10:30 Gastrointestinal Allergy.  
Dr. Merle M. Miller.
- 10:30–10:50 Classification and Differential Diagnosis of Chronic Diarrhea.  
Dr. Johnson.
- 10:50–11:05 Emotional Diarrhea.  
Dr. Tumen.
- 11:05–11:15 Intermission.
- 11:15–11:35 Bacillary and Salmonella Infections.  
Dr. Rush.
- 11:35–11:55 Amebic Dysentery.  
Dr. Hundley.
- 11:55–12:10 Physiology of Defecation.  
Dr. Comroe.
- 12:10–12:30 Functional Colonopathies.  
Dr. Willard.
- 12:30–1:00 Classification and Management of Constipation.  
Dr. Shay.
- P.M. Session—The Graduate Hospital.
- 2:15–2:45 Lymphogranuloma Venereum with Colonic Involvement:  
Clinical Features.  
Dr. Pessel.  
Roentgen Features.  
Dr. Finkelstein.
- 2:45–3:00 Radiation Injury of the Intestine.  
Drs. Hundley and Widmann.
- 3:00–3:30 Miller-Abbott Intubation in Intestinal Obstruction.  
Dr. Zintel.
- 3:30–3:40 Intermission.
- 3:40–4:10 Parietal Abdominal Neuralgia Simulating Appendicitis.  
Dr. Bates.
- 4:10–5:15 Presentation of Patients Illustrating Current Problems in Diagnosis  
and Treatment.  
Dr. Bockus and Colleagues.

*Tuesday, November 25.*

A.M. Session—Philadelphia General Hospital.

## CHRONIC NON-SPECIFIC ENTERITIS AND ENTEROCOLITIS

- 9:00- 9:25 Etiology and Classification of Types.  
Dr. Bockus.
- 9:25- 9:45 Clinical Features.  
Dr. Tumen.
- 9:45-10:00 Roentgen Diagnosis.  
Dr. Finkelstein.
- 10:00-10:15 Its Occurrence in Children.  
Dr. Ritter.
- 10:15-10:30 Medical Care and Indications for Operation  
Dr. Monaghan.
- 10:30-10:45 Operative Procedures.  
Dr. Ravdin.
- 10:45-11:00 Result of Operation and Prognosis.  
Dr. Johnson.
- 11:00-11:10 Intermission.
- 11:10-11:30 Intestinal Tuberculosis.  
Dr. Tumen.
- 11:30-12:00 Tumors of the Small Intestine.  
Drs. Bockus and Finkelstein.
- 12:00-12:20 Colonic Diverticulosis.  
Dr. Willard.
- 12:20-12:50 Diverticulitis vs. Carcinoma of the Sigmoid.  
Drs. Johnson and Zion.
- P.M. Session—The Graduate Hospital.
- 2:00- 2:30 Roentgen Studies in Intestinal Parasitosis.  
Dr. Keefer.

## CARCINOMA OF COLON

- 2:30- 2:50 Clinical Features.  
Dr. Shay.
- 2:50- 3:05 Sigmoidoscopy.  
Dr. Hundley.
- 3:05- 3:20 X-Ray.  
Dr. Widmann.
- 3:20- 3:40 Operative Procedures.  
Dr. Smyth.
- 3:40- 3:50 Intermission.
- 3:50- 5:00 Proctosigmoidoscopic Cinematography.  
Dr. Pessel.

*Wednesday, November 26.*

A.M. Session—Philadelphia General Hospital.

## NON-SPECIFIC ULCERATIVE COLITIS

- 9:00- 9:30 Classification of Types in Relation to Course of Disease.  
Dr. Bockus.
- 9:30-10:00 Role of Psychiatric Factors.  
Dr. Daniels.
- 10:00-10:15 Present Status of Chemotherapy and Antibiotics.  
Dr. Monaghan.

- 10:15-10:30 Indications for Operation.  
Dr. Tumen.
- 10:30-10:45 Operative Procedures.  
Dr. Ferguson.
- 10:45-11:00 Prognosis.  
Dr. Johnson.
- 11:00-11:10 Intermission.

FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT OF NEUROPSYCHIATRIC  
ORIGIN (Panel Discussion)

- 11:10-11:30 Alterations in the Function of the Colon in Man under Stress.  
Dr. Almy.
- 11:30-11:50 Functional Gastrointestinal Disturbances in Psychotic Reactions.  
Dr. Yaskin.
- 11:50-12:10 Functional Gastrointestinal Disturbance Associated with Psycho-  
neurotic Reactions.  
Dr. Weiss.
- 12:10-12:40 An Appraisal of the Role of the Psyche in Gastrointestinal Disease.  
Dr. T. Grier Miller.
- 12:40- 1:00 Questions and Answers.

COURSE NO. 12—GENERAL MEDICINE

(December 1-13, 1947)

*University of Texas School of Medicine, Galveston, Texas*

CHARLES T. STONE, M.D., F.A.C.P., *Director*

(Minimal Registration, 40; Maximal Registration, 50)

Fee: A.C.P. Members, \$60.00. Non-Members, \$120.00

*Officers of Instruction*

- Edgar V. Allen, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation;  
Chief of a Section in the Division of Medicine, Mayo Clinic; Rochester, Minn.
- John B. Barnwell, M.D., Chief, Tuberculosis Division, Veterans Administration,  
Washington, D. C.
- Truman G. Blocker, Jr., M.D., F.A.C.S., Professor of Plastic and Maxillofacial  
Surgery and Director, Postgraduate Division, University of Texas School of  
Medicine.
- Virginia Blocker, M.D., Lecturer in Medicine, University of Texas School of  
Medicine.
- Russell S. Boles, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University  
of Pennsylvania School of Medicine, Philadelphia, Pa.
- Paul Brindley, M.D., F.A.C.P., Professor of Pathology, University of Texas School  
of Medicine; Pathologist, John Sealy Hospital.
- M. Brucer, M.D., Instructor in Physiology, University of Texas School of Medicine.
- George E. Burch, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University  
of Louisiana School of Medicine, New Orleans, La.
- D. Bailey Calvin, Ph.D., Professor of Biological Chemistry and Dean of Students and  
Curricular Affairs, University of Texas School of Medicine.

- George M. Decherd, Jr., M.D., F.A.C.P., Associate Professor of Medicine and Director of Student Health Service, University of Texas.
- Donald Duncan, Ph.D., Professor of Anatomy, University of Texas School of Medicine.
- Jack R. Ewalt, M.D., Professor of Neuropsychiatry, University of Texas School of Medicine; Attending Neurologist and Psychiatrist, John Sealy Hospital; Director, Galveston State Psychopathic Hospital.
- Chester N. Frazier, M.D., F.A.C.P., Professor of Dermatology and Syphilology, University of Texas School of Medicine; Dermatologist and Syphilologist, John Sealy Hospital.
- Raymond L. Gregory, M.D., F.A.C.P., Professor of Medicine, University of Texas School of Medicine; Director, Outpatient Department, and Attending Physician, John Sealy Hospital.
- Edwin C. Hamblen, M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief of the Endocrine Division and Endocrinology, Duke University Hospital; Durham, N. C.
- Arild E. Hansen, M.D., Professor of Pediatrics, University of Texas School of Medicine.
- Albert W. Harrison, M.D., Assistant Professor of Chest Surgery, University of Texas School of Medicine.
- George R. Herrmann, M.D., F.A.C.P., Professor of Medicine and Director of the Cardiovascular Unit, University of Texas School of Medicine; Director, Latin-American Relations, University of Texas; Physician, John Sealy Hospital.
- Jesse B. Johnson, M.D., Associate Professor of Radiology, University of Texas School of Medicine.
- Chauncey D. Leake, Ph.D., Professor of Pharmacology, Vice President and Dean, University of Texas School of Medicine.
- William C. Levin, M.D., Assistant Professor of Medicine, University of Texas School of Medicine; Director, Blood Bank, John Sealy Hospital.
- Moise D. Levy, M.D., F.A.C.P., Lecturer in Medicine, University of Texas School of Medicine; A.C.P. Governor for Texas; Houston, Tex.
- William L. Marr, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Director of Allergy and Hematology Clinics and Attending Physician, John Sealy Hospital.
- John W. Middleton, M.D., Assistant Professor of Medicine and Director of Student Health Service, University of Texas School of Medicine.
- Carl V. Moore, Jr., M.D., F.A.C.P., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.
- Robert M. Moore, M.D., F.A.C.S., Professor of Surgery and Chairman, Department of Surgery, University of Texas School of Medicine.
- William W. Nesbitt, M.D., Commanding Officer, United States Marine Hospital, Galveston, Tex.
- Alton Ochsner, M.D., F.A.C.S., William Henderson Professor of Surgery and Director, Department of Surgery, Tulane University of Louisiana School of Medicine, New Orleans, La.
- Eric Ogden, M.R.C.S., L.R.C.P., Professor of Physiology, University of Texas School of Medicine.
- Teofilo Ortiz y Ramirez, M.D., Chief of Roentgenological Service, Instituto de Nacional Cardiologia, Mexico, D.F.
- Morris Pollard, D.V.M., M.S., Assistant Professor of Public Health and Preventive Medicine, University of Texas School of Medicine.

- Charles M. Pomerat, Ph.D., Professor of Cytology, University of Texas School of Medicine.
- Edward Randall, Jr., M.D., F.A.C.P., Professor of Therapeutics, University of Texas School of Medicine; Consulting Physician, John Sealy Hospital.
- Raymond H. Rigdon, M.D., Professor of Experimental Pathology, University of Texas School of Medicine.
- Arthur Ruskin, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Visiting Physician and Director, Heart Station, John Sealy Hospital.
- Martin Schneider, M.D., Associate Professor of Radiology, University of Texas School of Medicine; Director, Department of Radiology, John Sealy Hospital.
- Edward H. Schwab, M.D., F.A.C.P., Associate Professor of Medicine, University of Texas School of Medicine; Attending Physician, John Sealy Hospital.
- S. R. Snodgrass, M.D., F.A.C.S., Associate Professor of Neurosurgery, University of Texas School of Medicine.
- Demetrio Sodi y Pallares, M.D., Chief of the Electrocardiographic Service, Instituto de Nacional Cardiologia, Mexico, D.F.
- Mayo H. Soley, M.D., Associate Professor of Medicine and Assistant Dean, University of California Medical School, San Francisco, Calif.
- Charles T. Stone, M.D., F.A.C.P., Professor of Medicine and Chairman, Department of Internal Medicine, University of Texas School of Medicine; Physician-in-Chief, John Sealy Hospital.
- Willard O. Thompson, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.
- Martin L. Towler, M.D., Assistant Professor of Neurosurgery, University of Texas School of Medicine.
- Henry H. Turner, M.D., F.A.C.P., Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.
- Fredrick A. Willius, M.D., F.A.C.P., Professor of Medicine, Mayo Foundation; Senior Consultant, Section on Cardiology, Mayo Clinic, Rochester, Minn.
- Henry M. Winans, M.D., F.A.C.P., Clinical Professor of Medicine and Professor of Medical History, Southwestern Medical School, Dallas, Tex.
- Maxwell M. Wintrobe, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

This course will present present day concepts in practice, teaching and research in the more important fields of Internal Medicine. For example, two and a half days will be given to Cardiovascular Diseases, two days to Metabolic and Endocrine Diseases, two days to Hematology and one day each to the following: Infectious Diseases, Gastrointestinal Diseases and Diseases of the Chest. The modern applications of nuclear physics to medical practice and investigation will be presented by authorities in the field in relation to the particular conditions in which they are applicable.

The plan of the course is to have the presentations divided into several categories, for example, discussions and demonstrations before the class as a whole, ward rounds twice each week with small groups of the class, clinical pathological conferences weekly and two or more round table panel discussions.

If a sufficient number of the class desires, special demonstrations will be arranged for small groups in certain laboratory and technical subjects. For example, sternal marrow biopsy, supravital blood staining technics, the precordial leads in the electrocardiogram, tissue cultures, electric shock therapy, fever therapy and others can be arranged as electives at the time of scheduled ward rounds.

Announcement will be made of the availability of these special demonstrations at the beginning of the course, and the class will be polled with regard to its wishes.

*Hotel Accommodations:* When writing for accommodations, it will be necessary to identify oneself with the College and this particular course. Address the Manager (Mr. Sweat), Galvez Hotel, Galveston, or Mr. Jimmie Powledge, Manager, The Buccaneer Hotel, Galveston. Certain conferences will be held at the Galvez Hotel; on the other hand, the Buccaneer Hotel has promised us as many single rooms as desired. Both hotels are affiliated National Hotels.

### *Outline of Course*

*Monday, December 1.*

A.M. Session.

8:30- 9:15 Registration—Randall Hall, Fourth Floor, Outpatient Building, John Sealy Hospital.

9:15- 9:30 Introduction.

Dr. Charles T. Stone.

Dr. Chauncey D. Leake.

Dr. Truman G. Blocker, Jr.

### CARDIOVASCULAR DISEASES

Dr. Herrmann presiding

9:30-10:00 Cardiovascular Physiology.

Dr. Ogden.

10:00-10:30 Pathogenesis of Hypertension.

Dr. Gregory.

10:30-11:00 Surgical Treatment of Hypertension.

Dr. Snodgrass.

11:00-11:30 Hypertensive Vascular Disease.

Dr. Allen.

11:30-12:00 Hypertensive Heart Disease.

Dr. Herrmann.

P.M. Session.

Dr. Schwab presiding

2:00- 2:30 Renal Disease.

Dr. Burch.

2:30- 3:00 Pulmonary Embolism, Diagnosis and Medical Treatment.

Dr. Allen.

3:00- 3:30 Venous Thrombosis, Surgical Treatment.

Dr. Ochsner.

3:30- 4:00 Questions and Answers.

4:00- 4:30 The Use of Radioactive Sodium in the Study of Congestive Heart Failure.

Dr. Burch.

4:30- 5:00 Management of Congestive Heart Failure.

Dr. Burch.

*Tuesday, December 2.*

A.M. Session.

### CARDIOVASCULAR DISEASES (continued)

Dr. Schwab presiding

9:00- 9:30 The Normal Electrocardiogram.

Dr. Brucer.

- 9:30-10:30 Newer Concepts of Electrocardiography  
Dr. Sodi y Pallares.
- 10:30-11:00 Acute Myocardial Infarction.  
Dr. Schwab.
- 11:00-11:30 Certain Factors Influencing Survival or Death in Coronary Artery  
Disease.  
Dr. Willius.
- 11:30-12:30 Ward Rounds.  
P.M. Session.
- Dr. Stone presiding
- 2:00- 2:30 Congenital Heart Disease.  
Dr. Schwab.
- 2:30- 3:30 Cardiac Roentgenology and Angiocardiography.  
Dr. Ortiz y Ramirez.
- 3:30- 4:00 Surgical Treatment of Congenital Heart Disease.  
Dr. Harrison.
- 4:00- 5:00 Clinical Pathological Conference.  
Drs. Brindley, Rigdon and the Medical Staff.

*Wednesday, December 3.*

A.M. Session

#### CARDIOVASCULAR DISEASES (continued)

Dr. Randall presiding

- 9:00- 9:30 Syphilitic Heart Disease.  
Dr. Frazier.
- 9:30-10:00 Rheumatic Fever.  
Dr. Hansen.
- 10:00-10:30 Chorea and Its Treatment.  
Dr. Randall.
- 10:30-11:00 Rheumatic Heart Disease.  
Dr. Ortiz y Ramirez.
- 11:00-12:00 Ward Rounds.  
P.M. Session.

#### NUCLEAR PHYSICS

Dr. Decherd presiding

- 2:00- 2:30 Nuclear Physics and Its Application to Medicine.  
Dr. Soley.
- 2:30- 3:30 Radioactive Isotopes as Tracers.  
Dr. Soley.
- 3:30- 4:00 The Use of Antithyroid Drugs.  
Dr. Decherd.
- 4:00- 5:00 Radioactive Iodine in the Treatment of Graves' Disease and the Treat-  
ment of Tumors of the Thyroid.  
Dr. Soley.

*Thursday, December 4.*

A.M. Session.

#### HEMATOLOGY

Dr. Marr presiding

- 9:00- 9:45 The Reticulo-endothelial System.  
Dr. Pomerat.

9:45-10:45 The Present Status of Folic Acid.

Dr. Carl V. Moore.

10:45-12:00 Presentation of Cases.

Drs. Marr, Levin, Carl V. Moore and Wintrobe.

P.M. Session.

Dr. Marr presiding

2:00- 3:00 Pathogenesis of the Anemia of Infections.

Dr. Wintrobe.

3:00- 4:00 Radioactive Iron and Study of Iron Metabolism.

Dr. Carl V. Moore.

4:00- 4:30 Indications for Splenectomy.

Dr. Marr.

4:30- 5:00 Management of Refractory Anemias.

Dr. Wintrobe.

*Friday, December 5.*

A.M. Session.

#### HEMATOLOGY (continued)

Dr. Levin presiding

9:00- 9:45 Radioactive Phosphorus in the Treatment of Leukemia and Polycythemia.

Dr. Soley.

9:45-10:30 Use of Nitrogen Mustard in the Treatment of Leukemias. Hodgkin's Disease and Malignant Diseases.

Dr. Wintrobe.

10:30-11:15 Sickle-Cell Anemia.

Dr. Levin.

11:15-12:00 Clinical Pathological Conference.

Drs. Carl V. Moore and Brindley.

P.M. Session.

Dr. Stone presiding

2:00- 2:30 Cardiac Manifestations of Anemias.

Dr. Decherd.

2:30- 3:00 Effect of Anemias on Renal Function.

Drs. Gregory and Levin.

3:00- 3:30 Stethograph in the Appraisal of Heart Sounds.

Dr. Decherd.

3:30- 4:00 The Evaluation of Coronary Insufficiency.

Dr. Ruskin.

4:00- 5:00 Presentation of Patients.

Drs. Decherd, Ruskin and the Medical Staff.

*Saturday, December 6.*

A.M. Session.

Dr. Leake presiding

9:00-12:00 Dateline—Texas City, April 16, 1947. Medical Aspects.

Drs. Leake, Truman G. Blocker, Jr., Virginia Blocker, Ruskin and Levin.



*Monday, December 8.*

A.M. Session.

INFECTIOUS DISEASES

Dr. Moise D. Levy presiding

A.C.P. Governor for Texas

- 9:00- 9:30 Infectious Hepatitis.  
Dr. Stone.
- 9:30-10:15 Streptomycin in Therapy other than Tuberculosis.  
Dr. Winans.
- 10:15-11:00 Recent Advances in Virus Diseases.  
Dr. Pollard.
- 11:00-12:00 Recent Advances in Antibiotics and Chemotherapy.  
Dr. Leake.

P.M. Session.

- 2:00- 2:45 Endemic Typhus Fever.  
Dr. Levy.
- 2:45- 3:30 Brucellosis.  
Dr. Winans.
- 3:30- 4:15 Discussion of Virus Infection of the Central Nervous System.  
Dr. Ewalt.
- 4:15- 5:00 Experiences with Infectious Diseases in Natives of the Pacific Islands.  
Dr. Nesbitt.

*Tuesday, December 9.*

A.M. Session.

GASTRO-ENTEROLOGY

Dr. Stone presiding

- 9:00-10:30 Ward Rounds.
- 10:45-11:30 Hepatic Cirrhosis.  
Dr. Boles.
- 11:30-12:00 X-Ray Diagnosis in Gastrointestinal Diseases.  
Dr. Schneider.

P.M. Session.

- 2:00- 2:45 Recent Advances in Intestinal Infections.  
Dr. Winans.
- 2:45- 3:45 Peptic Ulcer.  
Dr. Boles.
- 3:45- 4:15 The Psychologic Basis of Gastrointestinal Diseases.  
Dr. Towler.
- 4:15- 5:00 Vagotomy.  
Dr. Robert M. Moore.

*Wednesday, December 10.*

A.M. Session.

GASTRO-ENTEROLOGY (continued)

Dr. Calvin presiding

- 9:00- 9:45 Recent Advances in Biochemistry and Their Clinical Implications.  
Dr. Calvin.
- 9:45-10:45 Chronic Ulcerative Colitis.  
Dr. Boles.

- 10:45-11:15 Presentation of Cases.  
Dr. Stone and Staff.
- 11:15-12:00 Gastric Cancer.  
Dr. Boles.
- P.M. Session.

## DISEASES OF THE CHEST

Dr. Middleton presiding

- 2:00- 2:45 Tuberculosis in General Hospitals.  
Dr. Barnwell.
- 2:45- 3:30 Suppurative Disease of the Lung.  
Dr. Middleton.
- 3:30- 4:15 Streptomycin in Treatment of Tuberculosis.  
Dr. Barnwell.
- 4:15- 5:00 Management of Pulmonary Suppuration.  
Drs. Middleton and Harrison.

*Thursday, December 11.*

A.M. Session.

## DISEASES OF THE CHEST (continued)

Dr. Middleton presiding

- 9:00- 9:45 Early Tuberculous Lesion.  
Dr. Barnwell.
- 9:45-10:30 Indications for Surgical Treatment of Tuberculosis.  
Dr. Harrison.
- 10:30-11:15 Spontaneous Pneumothorax.  
Dr. Barnwell.
- 11:15-11:35 The Principles of X-Ray Interpretation in Chest Diseases.  
Dr. Johnson.
- 11:35-12:00 Upper Abdominal Disease in Relation to Thoracic Disease.  
Dr. Gregory.

P.M. Session.

## ENDOCRINOLOGY AND METABOLISM

Dr. Gregory presiding

- 2:00- 3:00 Endocrine Functions of the Hypothalamus.  
Dr. Duncan.
- 3:00- 4:00 Management of Diabetic Acidosis and Complications.  
Dr. Gregory.
- 4:00- 4:30 Diagnosis and Treatment of Hypoglycemia.  
Dr. Gregory.
- 4:30- 5:00 Presentation of an Unusual Syndrome.  
Dr. Gregory.

*Friday, December 12.*

A.M. Session.

## ENDOCRINOLOGY AND METABOLISM (continued)

Dr. Randall presiding

- 9:00-10:00 Hypo-pubescence in the Male.  
Dr. Hamblen.

- 10:00-11:00 Endocrine Problems of the Aging.  
Dr. Thompson.
- 11:00-12:00 Pituitary Adreno-cortical Syndrome.  
Dr. Turner.
- P.M. Session.
- 2:00- 3:00 Pituitary Disorders and Their Treatment.  
Dr. Thompson.
- 3:00- 4:00 Therapeutic Limitation of Pituitary Hormones.  
Dr. Turner.
- 4:00- 5:00 Hypo-pubescence in the Female.  
Dr. Hamblen.

*Saturday, December 13.*

A.M. Session.

ENDOCRINOLOGY AND METABOLISM (continued)

Dr. Gregory presiding

- 9:00-10:00 Treatment of Obesity.  
Dr. Thompson.
- 10:00-11:00 Functional Irregularities of Uterine Bleeding.  
Dr. Hamblen.
- 11:00-12:00 Fatigue States Associated with Endocrine Disorders.  
Dr. Turner.

*OBITUARIES*

## DR. GUY HENRY FAGET

Guy Henry Faget, M.D., F.A.C.P., died July 17, 1947, at the U. S. Marine Hospital, New Orleans, La. Dr. Faget was widely known for his interest in tuberculosis, tropical diseases and, more recently, leprosy.

Dr. Faget was born in New Orleans, June 15, 1891. From the city's public schools he entered the Tulane University School of Medicine from which he received his medical degree in 1914. He interned in the U. S. Marine Hospital in that city; served as resident physician in the Presbyterian Hospital there in 1915-16; and, from 1916 to 1922, engaged in private practice and as health officer in the British Honduras. Dr. Faget became commissioned in the U. S. Public Health Service in 1922. His assignments from that date until 1940 included hospitals and stations in Mobile, San Francisco, Fort Stanton, New Orleans, and Norfolk. He served as Medical Officer in Charge of the National Leprosarium in Carville, La., from 1940 until very recently.

Dr. Faget was a member of the International Leprosy Association and, since 1941, a Fellow of the American College of Physicians.

## DR. CLEMENT COLEMAN FENTON

Clement Coleman Fenton, M.D., F.A.C.P., of Morgantown, W. Va., died May 28, 1947, at the age of 54. A widely known pathologist, Dr. Fenton had been a Fellow of the American College of Physicians since 1937.

Dr. Fenton was born in New York City in 1892. He received the A.B. degree from Columbia University in 1915, the B.A. and M.S. degrees from West Virginia University in 1922, and the M.D. degree from the Cornell University Medical College in 1925. Further studies of pathology were made at Columbia University, the University of Minnesota, Western Reserve University, and in Berlin and Vienna.

First appointed Instructor in Pathology in the West Virginia University School of Medicine in 1922, Dr. Fenton served as Professor of that subject from 1926 until the time of his death. He also was Pathologist to the City and Monongalia General Hospitals, Morgantown, and the Kercheval Memorial Clinic, Kingwood. Dr. Fenton had been a member of the Monongalia County and West Virginia Medical Societies, the Southern and American Medical Associations, and of the American Association of Pathologists and Bacteriologists, American Association for the Study of Neoplastic Diseases, and the International Association of Medical Museums.

EDWARD J. VAN LIERE, M.D., F.A.C.P.,

Morgantown, W. Va.

## DR. ROBERT EDWIN McBRIDE

Robert Edwin McBride, M.D., F.A.C.P., died January 17, 1947, at his home in Las Cruces, New Mexico, of cerebral hemorrhage one month short of 74 years of age. He was survived by nine children and, for only three months, by his wife, Genevieve.

Dr. McBride was born in Thibodaux, La. He attended the grade schools of LaFourche Parish, and the Medical Department of Tulane University from which he graduated in 1896.

After eight years of practice in Louisiana, Dr. McBride located at Las Cruces, N. M., in 1904. He became a member of the Staff of the Hotel Dieu in El Paso in 1920, and Medical Director of the McBride-Evans Clinic at Las Cruces in 1935.

Dr. McBride had been a member of the Dona Ana County and New Mexico Medical Societies and a Fellow of the American Medical Association since his location in Las Cruces. He was secretary of the New Mexico Medical Society from 1907 to 1908, and from 1910 to 1920. He served as editor of the New Mexico Medical Journal during that time, and later as editor for Southwestern Medicine. He was a member of the Episcopal Church.

Highly respected and regarded by the laity and profession alike, Dr. McBride was long a leader and a stimulus to the medical profession in the Southwest.

ROBERT O. BROWN, M.D., F.A.C.P.,  
Governor for New Mexico

## DR. CLAYTON ELBERT ROYCE

Clayton Elbert Royce, M.D., F.A.C.P., of Lutz, Fla., died February 12, 1947, of coronary occlusion. Dr. Royce had been a Fellow of the American College of Physicians since 1931.

Born at Woodstock, Vt., December 20, 1886, Dr. Royce attended Dartmouth College and the College of Physicians and Surgeons of Columbia University. He interned in pathology at the German Hospital, now Lennox Hill Hospital, N. Y. He subsequently served as Pathologist to the University Hospitals, Iowa City, Iowa, from 1912 to 1917; to St. Luke's Hospital, Bethlehem, Pa., from 1917 to 1929; and from 1929 to 1945 as Director of Laboratories, St. Vincent's Hospital, and Pathologist, Duval County Hospital, Jacksonville, Fla. Dr. Royce was a member of the Duval County Medical Society, the Florida Medical Association, American Medical Association, International Association of Medical Museums, and a former Counsellor of the American Society of Clinical Pathology.

## DR. WALTER HOBERT WATTERSON

Dr. Walter Hobert Watterson, F.A.C.P., of La Grange, Ill., died June 17, 1947.

Dr. Watterson was born near Fairbury, Ill., on February 12, 1875. He received his M.D. degree from Northwestern University Medical School in 1901. He subsequently served as Assistant Medical Director of the Y.M.C.A. Health Farm, Denver, Colo., 1904-05; as Medical Superintendent, Lake Breeze Sanatorium, Waukegan, 1908-13, and of Pokegama Sanatorium, Pine City, Minn., 1913-14; as Head Physician, Cook County Tuberculosis Hospital, 1915-17; and as Medical Superintendent, Municipal Tuberculosis Sanitarium, Chicago, 1917-18. During the first World War, Dr. Watterson attained the rank of Major in the Army and served as Medical Chief of U. S. General Hospitals No. 16, New Haven, Conn.; No. 18, Waynesville, N. C.; and No. 42, Spartanburg, S. C. Returning to Illinois, he became Chief of Tuberculosis Service, Veterans Administration Facility, Hines, 1923-29. Dr. Watterson also was Medical Director of the Zace Sanatorium, Winfield, 1927-36, and Consultant, 1936-47; and was Consultant on the Staffs of West Lake Hospital, Melrose Park, and of Hinsdale Sanatorium.

Dr. Watterson was a member and a former Secretary-Treasurer, President, and Trustee of the Chicago Tuberculosis Society. He was also a member of the Illinois Trudeau Society, the National Tuberculosis Association, and of the Chicago and Illinois State Medical Societies. He was a Fellow of the American Medical Association and of the American College of Physicians (1929).

This resumé of Dr. Watterson's career fails to give adequate information regarding the man himself, his methods, his personality and his character. Dr. Watterson enjoyed, for nearly a half century, a full life of honorable, active service in medicine. He belonged to the old school of physical diagnosticians who depended so much upon the refined training of the special senses. Nevertheless he took the newer developments in stride and kept abreast with the changing trends and methods.

The principal feature of Dr. Watterson's character was his kindly, tolerant attitude and his ability to make friends. He was not in the least arrogant, domineering or vindictive, but was patiently insistent, and, if necessary, compellingly firm. He was a tireless worker and a respected teacher of young men; he commanded the respect of both his superiors and his subordinates. He made many valuable contributions to medical literature.

The medical profession has lost an able physician and his numerous co-workers have lost a loyal friend.

HENRY C. SWEANY, M.D., F.A.C.P.,

Chicago, Ill.

## DR. FREDERICK WOOTEN WILKERSON

Dr. Frederick Wooten Wilkerson, F.A.C.P., died April 24, 1947, of hypertensive cardiovascular disease, after a prolonged illness.

Son of Dr. William W. Wilkerson, he was born August 19, 1885, at Montgomery, Ala., where he resided throughout his life. He attended the University of Virginia for his academic education and was graduated in medicine from Columbia University College of Physicians and Surgeons in 1909. A diplomate of the American Board of Internal Medicine, Dr. Wilkerson was for many years attending physician, St. Margaret's Hospital, Montgomery. Dr. Wilkerson was a Fellow and a former member of the House of Delegates of the American Medical Association. He had served the Medical Association of the State of Alabama as a member of the Board of Censors and as a President. He was a member of the Montgomery County Medical Society, Southern Medical Association, American Heart Association, and of the Southern Interurban Clinical Club. Dr. Wilkerson was a Trustee of the Alabama Insane Asylum.

Elected to Fellowship in the American College of Physicians in 1930, Dr. Wilkerson performed valuable service as Governor for Alabama from 1931 to 1945.

Dr. Wilkerson had a keen interest in organized medicine and served it well. He served his country during World War I. His greatest contribution to society was the love and service he gave to his own community. Those who were closest to him loved him the most.

E. DICE LINEBERRY, M.D., F.A.C.P.,  
Governor for Alabama

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## HYPERVENTILATION: ANALYSIS OF CLINICAL SYMPTOMATOLOGY \*

By GEORGE L. ENGEL, M.D.,† EUGENE B. FERRIS, M.D., F.A.C.P., and  
MYRTLE LOGAN, M.D.,† *Cincinnati, Ohio*

HYPERVENTILATION is a common enough occurrence in clinical practice to justify further study of this phenomenon. Although the symptoms of hyperventilation are well known they are often overlooked because patients seldom complain of overbreathing, per se, and seldom exhibit tetany, the best known, but least common manifestation. Most often hyperventilation is psychogenic in origin. Thus, it may occur as a more or less non-specific reaction to the experience of terror, extreme anger, severe pain, or other intense emotions in essentially healthy individuals or it may be a symptom of neurosis. It occurs quite frequently during real anxiety and in the anxiety attacks of anxiety neurosis where it represents a physiologic concomitant of the anxiety. Physiologically, it serves the purpose of preparation for fight or flight, permitting prolonged physical exertion and even breathholding. A sensation of suffocation or smothering is a common occurrence during anxiety and may give rise to overbreathing of which the patient is unaware. In other instances, hyperventilation represents an hysterical conversion symptom, effecting the relief of an emotional tension in a more symbolic way. In such instances the overventilation may represent the expression of a repressed wish for sexual intercourse, or repressed hostility. Both mechanisms may be seen in the same patient.

Hyperventilation may also be observed during encephalopathies of a variety of causes and as a response to certain drugs, notably the salicylates.<sup>1</sup> And finally, hyperventilation is of practical significance at high altitude,

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† Now at Strong Memorial Hospital, Rochester, N. Y.



where the physiologic effects of anoxia provoke overbreathing through reflex mechanisms.

*Symptomatology:* The symptoms developing during hyperventilation are much the same regardless of the etiology and may be reproduced in any person by voluntary hyperventilation. They include numbness and tingling of the hands, feet, and face; buzzing in the head; varying degrees of reduction in the level of consciousness, described as dizziness, light-headedness, giddiness or faintness; blurring of vision; dryness of the mouth; stiffness of the muscles and tetany. When there is reduction in the level of consciousness there is often release of other neurotic patterns, such as increased anxiety, panic, weeping, and various hysterical reactions. As anyone who has tried it can testify, hyperventilation is an exceedingly fatiguing activity and many patients who experience involuntary hyperventilation complain of severe fatigue and exhaustion.

The hyperventilating patient most often complains of fainting, convulsions or of attacks of breathlessness or smothering. Many of the latter type patients believe they have heart disease. Few patients are aware of overbreathing, though some will note excessive sighing or yawning. Among the patients who complain of "spells" careful history will usually reveal that numbness, tingling, lightheadedness, giddiness, blurring of vision, and sometimes a sense of breathlessness will precede the actual loss of consciousness by several minutes. Often the patients do not fall but experience a sense of impending loss of consciousness for some minutes. Some patients describe sensations of unreality or floating as the level of consciousness is reduced. These symptoms may occur in any position, and may continue for long periods of time, fluctuating in intensity as periods of hyperpnea alternating with periods of relative apnea. The longer the hyperventilation continues the more likely is tetany to appear, with its subjective symptoms of stiffness and cramping of the extremities.

In the literature it has been generally assumed that these various symptoms are of the same origin. It will be one purpose of this report to demonstrate that although alkalosis is the common denominator there are two more or less unrelated groups of symptoms, one related to the reduction in consciousness and one related to tetany. That is, some symptoms are central and some peripheral in origin.

The symptoms can always be reproduced by voluntary hyperventilation, although we have found that they may be modified in a number of ways. In general, the length of time that a person can carry out voluntary hyperventilation continuously is determined by one of three factors: loss of consciousness upon which the subject generally stops breathing involuntarily, resuming as the level of consciousness returns; tetany, which eventually limits the motion of the respiratory musculature; and fatigue. As is well known, a prolonged period of involuntary apnea may follow a period of hyperventilation.

*Methods and Material:* Medical students and staff members, all between the ages of 20 to 35 years, volunteered for these experiments. In addition, patients with this syndrome have been studied. The subjects were instructed to hyperventilate maximally for the designated period of time during which observations were made.

Bipolar fronto-occipital electroencephalograms were obtained by means of a Grass 3-channel instrument. The mean frequency of the brain waves was determined for successive 10 second periods by the method described in previous publications.<sup>2,3</sup> The number of waves per second interval in 10 second intervals was counted, and from this a mean frequency for each 10 second period was calculated. This yielded a very satisfactory quantitative estimate of the progressive frequency changes during hyperventilation and provided more information than did the determination of a frequency spectrum for the whole period of hyperventilation.<sup>2</sup> Another method of expression was to calculate the mean frequency for the entire period of hyperventilation. Because of the greater accuracy of analysis, subjects were selected whose control records showed a high percentage of countable frequencies.

Blood sugar was determined by the Folin-Wu colorimetric method.

The effects of varying oxygen tensions were studied by hyperventilating at ground level (747 mm. Hg) and at a simulated altitude of 16,000 feet (412 mm. Hg) in the decompression chamber and by hyperventilation with 10 per cent oxygen-90 per cent nitrogen mixture inhaled through a Bulbularian type 14 demand mask modified for constant flow. The mask was equipped with a large balloon as a reservoir and the rate of flow was kept such that the rubber bag never collapsed. Each gas mixture was breathed for 10 minutes before hyperventilation was begun and 20 minutes were allowed for recovery from each period of hyperventilation. The order in which the different gas mixtures and different altitudes were tested was varied.

The effects of posture were tested on the tilt table. Pulse was recorded with the electroencephalograph. The subject stood motionless for from 15 to 30 minutes before hyperventilating to rule out any postural hypotension.

The level of consciousness was determined by presenting the subject with three objects to remember and a problem of multiplication to carry out during the last 30 seconds of a three-minute period of hyperventilation. As soon as the hyperventilation period was completed the subject was asked for the test material. One point was allowed for each correct response, giving a maximum score of six and a minimum of zero (no awareness that any test was given or no memory of any of the tests).

The effects of nitroglycerine, amyl nitrite, nicotinic acid, and calcium chloride were tested during successive periods of hyperventilation, on the same subjects, allowing 20 minutes for recovery between each experiment. Calcium chloride was given last.

## RESULTS

1. *Rate of Change in Arterial Blood During Hyperventilation.*

The changes in the arterial blood constituents will be discussed in more detail in another paper.<sup>4</sup> However, brief comment on the rate of change of the CO<sub>2</sub> content and tension and of the pH of blood during vigorous hyperventilation is pertinent at this time. The greatest part of the change in arterial CO<sub>2</sub> content is accomplished in the first 30 to 60 seconds of hyperventilation. The changes in CO<sub>2</sub> tension and in pH are also more rapid during the first 30 to 60 seconds, but less so than the rate of change of the CO<sub>2</sub> content. A single deep inspiration and expiration will reduce the CO<sub>2</sub> content by 5 to 7 volumes per cent and the CO<sub>2</sub> tension by 7 to 16 mm. Hg.<sup>5</sup> After the first minute, continued vigorous hyperventilation will lower CO<sub>2</sub> content only slightly. With different rates of hyperventilation, the rate of fall of CO<sub>2</sub> changed slightly but the eventual degree of reduction was about the same. These points are amply illustrated in the tables and charts of the papers referred to.<sup>4, 5</sup>

2. *Correlation Between Slowing of the Electroencephalogram and Level of Consciousness.*

When the level of consciousness was determined by testing the subjects' memory and ability to calculate during the last 30 seconds of a 180 second period of hyperventilation, it was found that there was a close correlation between the degree of reduction of awareness and the degree of slowing of frequency of the electroencephalogram. These results are illustrated in table 1 and figure 1, which also demonstrate the electroencephalographic frequency change during hyperventilation at varying oxygen tensions. In general, it was found that marked reduction in consciousness occurred when the electroencephalographic mean frequency was reduced to less than 5.0 cycles per second. If the subject was not unconscious at 150 seconds when the test of awareness was administered there was some tendency for depth of ventilation to diminish and electroencephalographic mean frequency to rise as the subject tried to concentrate on the task. Sometimes, when unconscious, the subject stopped breathing involuntarily.

Subjectively the symptoms described were essentially the same as those described by patients. However, it was of interest that when reduction in consciousness was marked the subject usually had no memory afterwards of having lost consciousness, merely feeling that the period of hyperventilation had been shorter than usual. In general, the more marked the reduction in consciousness, the less were the numbness and tingling and the less likely was tetany to appear. Usually if considerable slowing of the electroencephalogram and reduction in consciousness had not appeared by the end of three minutes of vigorous hyperventilation it was unlikely to appear, and the longer hyperventilation continued, the more likely was tetany to develop. None of the subjects fell while unconscious.



TABLE I (Continued)

Name	Gas Mixture	Electroencephalographic Mean Frequency Change during Hyperventilation																	Blood Sugar mg. %	Level of Awareness 150-180 sec. (0-6)		
		Time of Hyperventilation in Seconds																				
		Resting	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180				
M. S.	10% O <sub>2</sub>	11.7	11.3		10.7		9.4		8.3		6.9		7.5		7.8		9.9		60	6		
	Air	11.7	11.9		11.4		11.7		11.3		11.3		11.2		10.6		10.8				62	6
	100% O <sub>2</sub>	11.7	11.5		12.0		11.4		11.8		11.6		11.6		11.6		11.9					
M. L.	10% O <sub>2</sub>	8.8	8.9		8.9		8.4		7.3		5.0		4.6		4.4		5.5		60	6		
	Air	9.1	9.2		8.9		9.0		8.6		8.4		8.5		7.8		7.8				62	6
	100% O <sub>2</sub>	9.4		9.6		9.3		9.3		9.1		9.2		8.9		9.1		8.8				
W. S.	10% O <sub>2</sub>	10.3	9.8		9.8		9.5		9.0		8.8		8.5		8.6		9.5		81	6		
	Air	10.4	10.1		10.2		10.1		10.1		9.5		9.8		9.4		10.4				75	6
	100% O <sub>2</sub>	10.6	10.2		10.3		10.1		10.3		10.2		10.3		10.0		9.9					
W. P.	10% O <sub>2</sub>	10.0	9.0		8.9		7.5		4.8		3.3		4.1		2.9		3.3		75	0		
	Air	10.2	9.1		9.1		8.0		7.4		6.1		5.2		3.9		3.1				76	3
	100% O <sub>2</sub>	10.0	9.5		9.4		9.2		8.0		9.0		8.3		7.7		7.6					
H. K.	10% O <sub>2</sub>	9.6	8.9		8.5		8.1		7.9				7.6		7.5		7.7		90	4		
	Air	10.0	9.8		9.8		9.2		8.9		8.6		8.2		8.7		8.2				80	4
	100% O <sub>2</sub>	10.3	9.8		9.9		9.5		9.7		9.3		9.7		9.5		9.5					

Reduction in consciousness during hyperventilation had already been noted by Davis and Davis<sup>6</sup> who also observed a correlation with the appearance of delta waves. These results are also consistent with earlier studies of delirium in which it was demonstrated that the degree of reduction in consciousness in the acutely delirious patient correlated well with the degree of slowing of the electroencephalogram.<sup>7</sup>

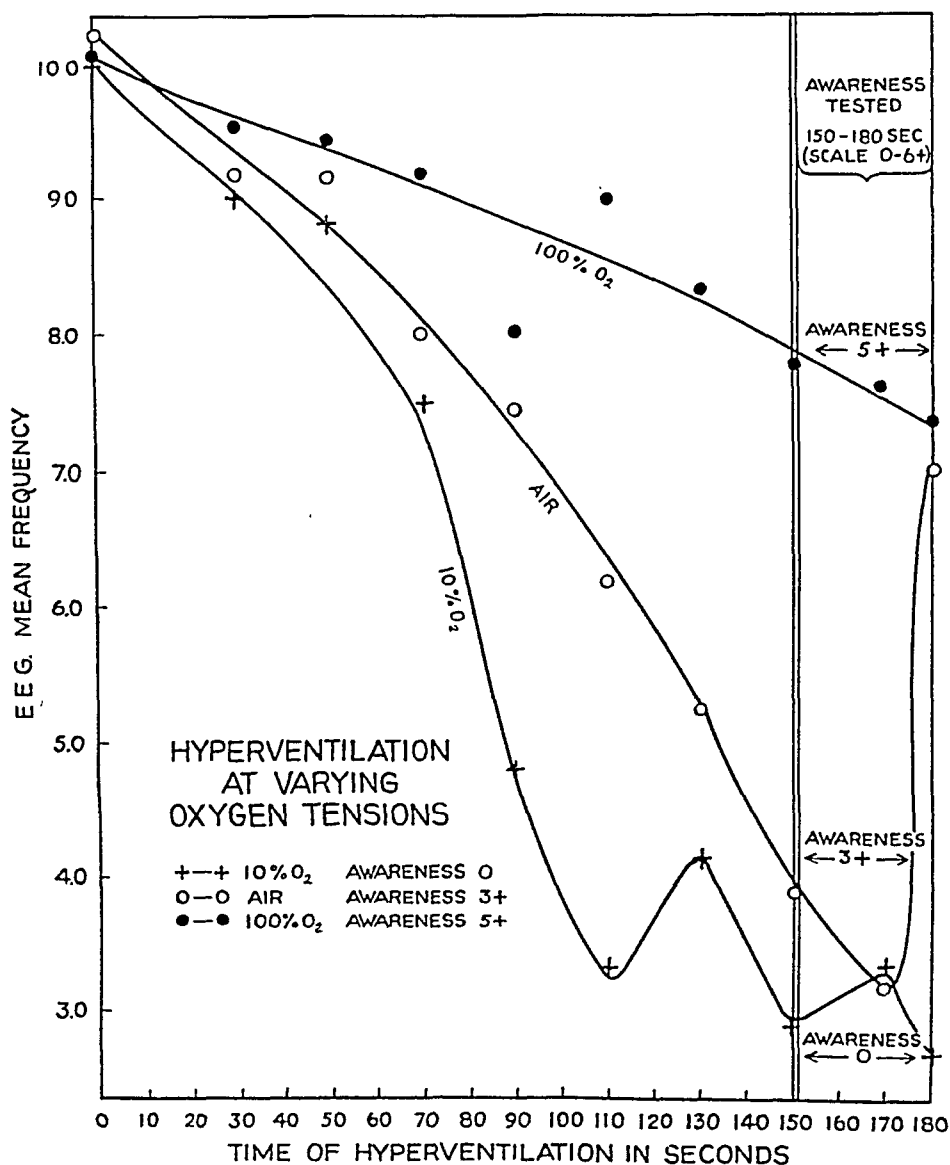


FIG. 1. E.E.G. mean frequency changes during hyperventilation at different oxygen tensions. Correlation with level of awareness.

### 3. Factors Influencing the Degree of Slowing of the Electroencephalogram.

Having established a correlation between the slowing of the electroencephalogram and level of consciousness, it becomes of importance to

delineate some of the factors influencing the amount of slowing during comparable degrees of acapnia. Repeated studies of arterial blood on the same subject during hyperventilation indicate that a coöperative subject achieves approximately the same degree of reduction in arterial  $\text{CO}_2$  each time.

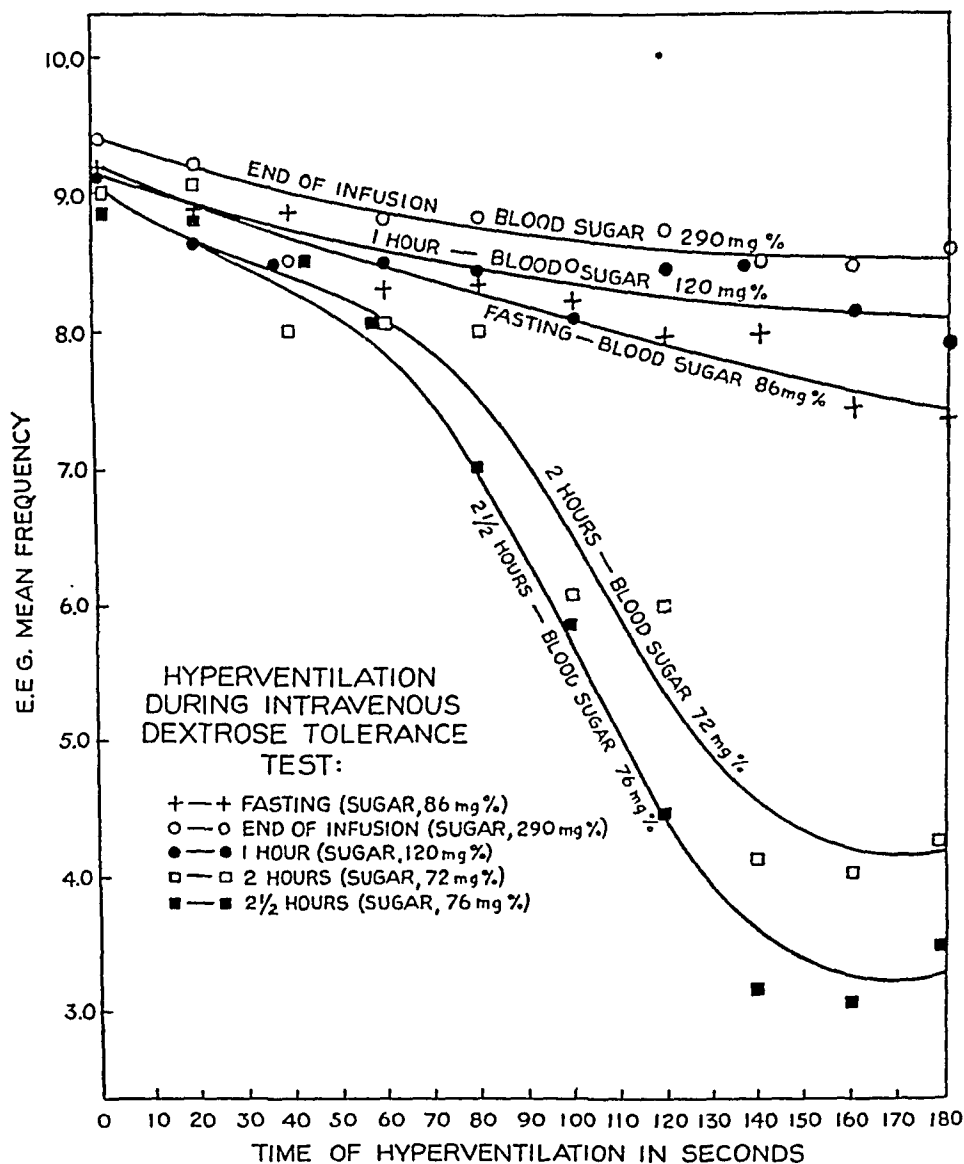


FIG. 2. E.E.G. mean frequency change at different blood sugar levels.

(a) *Individual Differences:* When other factors are controlled there still is a considerable difference among normal individuals as regards the ease with which slowing of the electroencephalogram develops during hyperventilation. However, all subjects seem to respond in the same direction to the various known factors which influence electroencephalographic frequency during hyperventilation. The factors concerned in this individual variation

have yet to be established. They do not appear to be related to the character of the resting electroencephalogram.

(b) *Age*: The degree of slowing is greatest in children and young adults, decreasing with age and levelling off after about age 35 years.<sup>8</sup> The younger patient is thus more likely to develop disturbance in consciousness during hyperventilation.

(c) *Rate of Hyperventilation*: The rate at which arterial  $\text{CO}_2$  is reduced seems to be of importance. Although a wide range of hyperventilation rates will reduce the arterial  $\text{CO}_2$  tension to about the same level, the more rapidly the  $\text{CO}_2$  is reduced the greater the slowing is likely to be.<sup>4</sup>

(d) *Blood Sugar*: The discovery that there was a correlation between the degree of electroencephalographic slowing during hyperventilation and the level of blood sugar was made simultaneously by a number of observers and has been the subject of many reports.<sup>9</sup> In figure 2 are illustrated the progressive electroencephalographic mean frequency changes at various points during an intravenous dextrose tolerance test. It will be noted in the data obtained on this subject that at the high blood sugar levels the rate of slowing during three minutes of hyperventilation was slight, while at the lowest blood sugar levels (72 and 76 mg. per cent) the slowing was marked. In

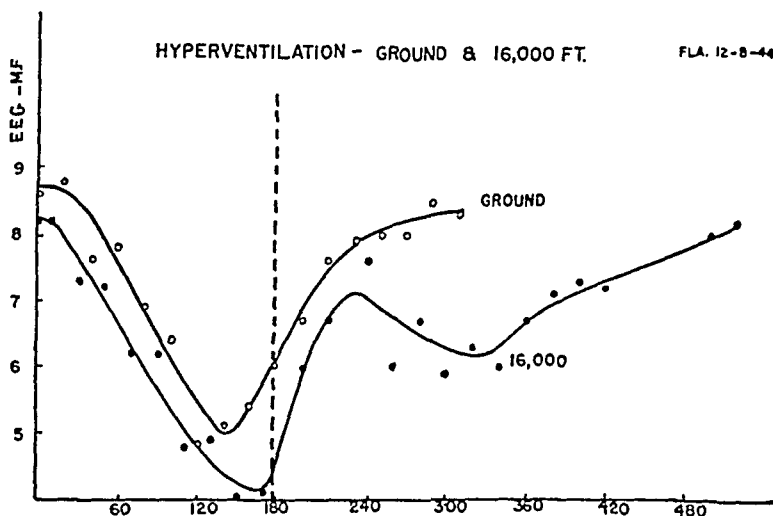


FIG. 3. Delay in recovery at 16,000 feet as compared to ground level.

general it has been found that significant slowing may be produced in the electroencephalogram of any normal individual if the blood sugar is reduced low enough, while blood sugar of 130 mg. per cent or higher will serve to eliminate significant slowing in most individuals. The intravenous injection of dextrose was not found to modify in any way the acid base balance of arterial blood during hyperventilation.<sup>2</sup>

With lower blood sugars where there is greater slowing of the electroencephalogram there is greater reduction in consciousness; with high blood sugar the subject can hyperventilate for longer periods and tetany is more likely to develop.







(e) *Oxygen Tension of Inspired Air*: The relationship between the degree of electroencephalographic slowing and the oxygen tension of the inspired air is illustrated in tables 1 and 2 and figures 1 and 3. The slowing of the electroencephalogram was most marked with 10 per cent oxygen-90 per cent nitrogen mixture (table 1) and at simulated altitude of 16,000 ft. (412 mm. Hg) (table 2) breathing air, and least marked when inspiring 100 per cent oxygen. Also, the rate of return to control frequency was much slower at 16,000 ft. (412 mm. Hg) than at ground level (747 mm. Hg) (table 2) (figure 3). When 100 per cent oxygen was substituted after hyperventilation for two minutes with air, further slowing of the electroencephalogram was inhibited (table 3). The amount of slowing and of change in consciousness at high altitude or with low oxygen mixtures could not be accounted for on the basis of the effects of anoxia alone. The effect of this degree of anoxia on the electroencephalogram has already been studied and found to be slight as compared to the effects noted here.<sup>3</sup>

That hyperventilation could be carried out more comfortably with oxygen was first noted by Hill and Flack in 1910.<sup>10</sup> Davis and Wallace made similar observations.<sup>9b</sup>

(f) *Posture*: Slowing of the electroencephalogram during hyperventilation is greater in the erect position as compared to the recumbent. This has already been reported elsewhere<sup>2</sup> and is illustrated in table 4 and figure 4. Table 4 shows the mean frequency for a 180 second period of hyperventilation in both positions (4 subjects, 10 experiments) and the maximum pulse and minimum blood pressure during hyperventilation in each position. The increase in slowing is not correlated with any consistent fall in blood pressure in the erect as compared to the recumbent positions and hence cannot be accounted for on the basis of hypotension and a related decreased cerebral blood flow. However, the acceleration in pulse rate during hyperventilation was consistently greater in the erect position, the heart rate exceeding 130 per minute in four of the 10 experiments. The maximum pulse rate during hyperventilation in the erect position was 156 per minute; in the recumbent position, 126 per minute.

This correlation between heart rate and increased slowing of the electroencephalogram is consistent with the findings of Darrow<sup>11</sup> who observed tachycardia to be more pronounced among the subjects with more marked slowing.

(g) *Effects of Amyl Nitrite, Nitroglycerine, and Nicotinic Acid*: Because Schwab has stated that amyl nitrite, by its action as a cerebral vasodilator, eliminates the slow activity of hyperventilation it was thought pertinent to check this observation.<sup>12</sup> Two subjects were given amyl nitrite by inhalation and nitroglycerine sublingually while recumbent. After allowing 20 minutes to recover from a control hyperventilation, each drug was given at 20 minute intervals in separate experiments and the hyperventilation begun after objective evidences of drug effect had developed. As can be

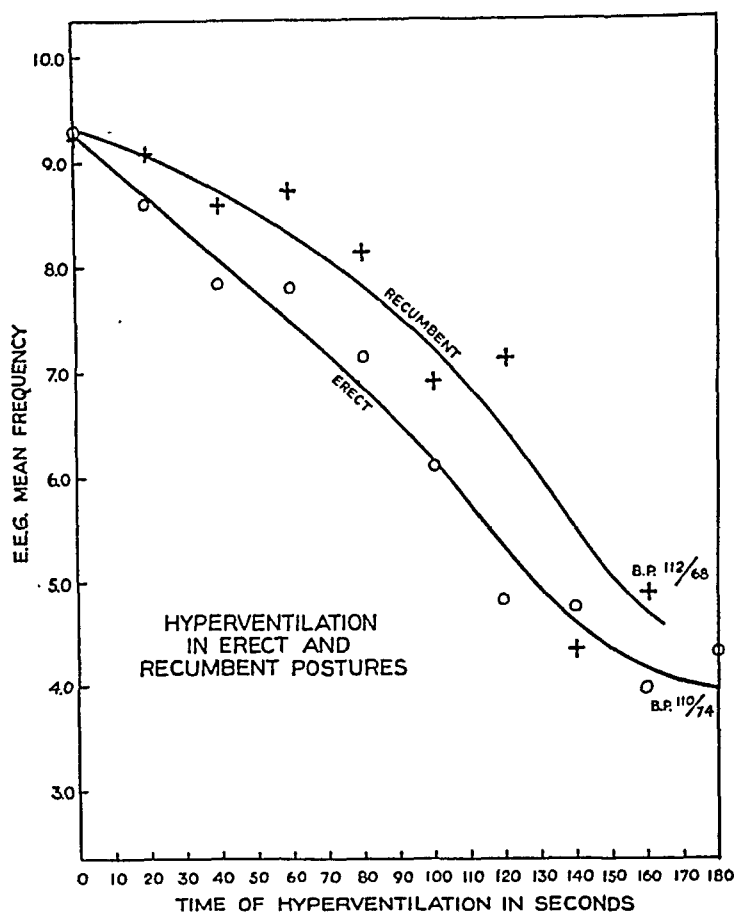


FIG. 4. Effect of hyperventilation on erect and recumbent position on E.E.G. mean frequency.

TABLE IV

Change in Electroencephalographic Mean Frequency, Pulse and Blood Pressure During Hyperventilation in the Recumbent and Erect Position

Subject	EEG (Mean Fre- quency) for 180 Sec. Period of Hyper- ventilation	Erect	Pulse (Maximum)	Erect	Blood Pressure (Minimum)	Erect	Blood Sugar mg. %
		Recumbent	Recumbent		Recumbent		
G. E. (1)	6.72	5.90	102	138	90/68	100/64	103
G. E. (2)	6.14	5.32	114	126	110/60	106/86	91
G. E. (3)	7.19	6.14	120	150	104/60	98/60	104
E. F. (1)	7.41	6.44	126	156	112/80	116/84	100
J. R. (1)	7.50	6.97	114	132	110/60	108/88	95
J. R. (2)	8.05	7.00	96	120	100/66	94/76	100
J. R. (3)	8.37	7.23	114	126	105/68	100/88	119
J. R. (4)	7.72	6.60	90	102	114/68	96/80	87
H. R. (1)	5.28	4.38	108	120	110/—	108/—	102
H. R. (2)	8.31	5.49	84	114	100/50	90/70	—

seen from table 5, there was a slight but significant increase in slowing during the period of activity of the drugs as compared to the control hyperventilation period.

In four experiments amyl nitrite was administered after the slow activity had become well established. In no instance was there any tendency for slow activity to diminish after the effect of the drug had made itself manifest

TABLE V  
Effect of Nitroglycerine, Amyl Nitrite, and Nicotinic Acid on Electroencephalogram During Hyperventilation

Subject	Condition	EEG Mean Frequency									Blood Sugar mg. %	Comment
		Time of Hyperventilation in Seconds										
		Rest- ing	30	50	70	90	110	130	150	170		
1	Control	8.8	8.5	8.2	8.3	5.0	5.1	4.2	4.3	3.8		
	Nitroglycerine 0.4 mg. (sublingual)	8.6	8.8	7.6	5.7	3.1	3.6	3.8	2.9	3.6		Flush
	Nitroglycerine 0.8 mg. (sublingual)	8.3	8.5	8.4	5.8	4.2	3.8	4.0	3.0	4.3	75	Pounding in head
	Control	9.0	9.3	9.0	8.4	6.0	3.7	4.1	4.1	4.5	77	Flush
	Amyl nitrite	9.3	9.5	8.0	5.3	4.8	3.0	4.8	4.3	3.4	84	Pounding in head
2	Control	9.6	9.5	9.1	8.6	8.8	8.3	6.7	7.0	7.0	68	Flush
	Nitroglycerine 0.8 mg. (sublingual)	9.7	9.5	8.5	8.7	6.6	6.9	6.5	5.0	5.6	78	Pounding in head
	Amyl nitrite	9.8	8.8	8.7	8.5	8.3	8.0	5.6	7.1	4.5	77	Flush—pounding in head. H.V. less adequate
3	Control	10.8	10.4	10.5	9.2	5.5	4.9	5.2	6.4	4.5	109	
	Nicotinic acid 100 mg. i.v.	11.0	10.0	9.8	8.7	5.6	5.0	4.5	4.1	4.8	102	
	Control	10.7	9.5	9.5	8.6	4.5	4.8	6.2	5.1	4.9	99	Marked flush
4	Control	10.3	10.0	10.4	7.4	5.6	4.7	4.0	3.1	4.6	95	
	Nicotinic acid 100 mg. i.v.	11.1	10.3	10.4	6.0	4.7	4.9	4.6	3.0	3.5	106	Marked flush
5	Control	10.9	11.2	10.7	10.8	10.1	10.6	9.9	10.4	9.8	148	
	Nicotinic acid 100 mg. i.v.	10.9	10.1	10.7	10.9	9.9	10.5	9.7	10.2	9.5	126	Severe flush Swelling of face

by the flushing of the face. In two subjects the pungent odor at first inhibited respiration for about 10 seconds and this was associated with some acceleration of the electroencephalogram, but this was transient, the slow activity resuming as soon as hyperventilation was resumed. It was difficult to establish whether there was increase in slow activity in this type of experiment.

Nicotinic acid (100 mg.) was administered intravenously to three subjects and hyperventilation begun when the flush had become well established.

There was no significant effect on the rate of slowing of the electroencephalogram.

Changes in symptoms could not be evaluated because of the side effect of the drugs themselves. In general reduction in consciousness seemed to be greater with amyl nitrite and nitroglycerine than with the control hyperventilation.

Of the three drugs used amyl nitrite probably produced the most marked increase in intracranial blood flow and nicotinic acid the least.<sup>13</sup> The magnitude of hyperventilation change in the electroencephalogram produced by these drugs, as compared to the effects of blood sugar and oxygen tension, is small and would suggest that vascular factors are not primary. Other studies support this suggestion.<sup>4</sup>

(h) *Effects of Calcium*: It is generally thought that the intravenous injection of calcium will prevent or diminish hyperventilation tetany, but the literature on this point is actually very unsatisfactory.<sup>14</sup> Although most investigators claim this to be so, we found only two cases reported in which susceptibility to tetany was recorded before and after the injection of calcium. O'Donovan found it effective in his case, while Schultzer and Lebel found it ineffective, in spite of raising the serum calcium from 10.5 mg. per cent to 12.0 mg. per cent.<sup>14</sup> There are no statements in the literature relevant to the effects of calcium on the disturbances in consciousness.

TABLE VI

Effect of Intravenous Calcium Chloride on Electroencephalogram During Hyperventilation

Subject	Conditions	EEG Mean Frequency									Blood Sugar mg. %	Comment
		Time of Hyperventilation in Seconds										
		Rest-ing	30	50	70	90	110	130	150	170		
1	Control CaCl <sub>2</sub> .75 gm. i.v.	10.7	9.5	9.5	8.6	4.5	4.8	6.2	5.1	4.9	99	Sl. Nausea
		10.6	10.1	9.6	9.3	8.7	5.3	6.6	6.5	4.3	113	
2	Control CaCl <sub>2</sub> 1.0 gm. i.v.	10.6	10.8	9.6	9.8	8.7	8.2	7.8	7.2	7.4	94	
		10.8	10.5	10.4	10.3	10.4	10.4	9.8	8.9	9.4	131	
3	Control CaCl <sub>2</sub> 1.0 mg. i.v.	10.7	10.7	10.2	8.9	7.0	5.8	5.3	5.9	3.2	95	
		10.8	10.7	10.3	8.8	8.1	6.7	3.4	3.8	3.1	106	

Three subjects hyperventilated before and again after receiving from 0.7 to 1.0 gm. calcium chloride intravenously (table 6). There was a slight tendency for less slowing after the calcium, but this could be adequately accounted for by the change in blood sugar. Two subjects noted less tingling during the hyperventilation after the calcium injection.

impossible to control ventilation voluntarily by mechanical devices so that only an optimum degree of reduction in  $p\text{CO}_2$  is produced, the danger of acapnia is ever present. Otis, Rahn, Epstein and Fenn<sup>20</sup> using the Hecht Visual Contrast Discrimination Test and a hand steadiness test have confirmed our observations indicating that the effects of anoxia and acapnia are additive in most zones.

### SUMMARY

1. Hyperventilation may occur as a response to certain intense emotional experiences in normal people, as a vegetative neurotic symptom, as a hysterical symptom, as a symptom of diffuse encephalopathy and certain drugs, and as a response to anoxia.

2. The symptoms may be divided into those related to reduction in consciousness and those related to tetany.

3. Reduction in consciousness is found to correlate well with the degree of slowing of the electroencephalogram and is usually marked when the mean frequency is reduced below 5.0 per second.

4. Slowing of E.E.G. frequency during hyperventilation is more marked with:

- (a) rapid reduction in arterial  $\text{CO}_2$  content
- (b) low blood sugar
- (c) low oxygen tension of inspired air
- (d) the erect posture
- (e) amyl nitrite and nitroglycerine.

Conversely, high blood sugar, high oxygen tension, and the recumbent posture diminish E.E.G. slowing.

5. Intravenous injection of calcium chloride and nicotinic acid has no effect on E.E.G. during hyperventilation.

6. Tetany is unrelated to changes in E.E.G. and occurs with longer periods of hyperventilation. The numbness and tingling probably are also peripheral in origin.

7. Actual syncope is unusual during hyperventilation. Four different mechanisms have been observed:

- (a) concurrent or delayed vasodepressor syncope
- (b) accentuation of already present orthostatic hypotension
- (c) hysterical syncope
- (d) central type.

### BIBLIOGRAPHY

- 1a. RYDER, H. W., SHAVER, M., and FERRIS, E. B.: Salicylism accompanied by respiratory alkalosis and toxic encephalopathy, *New Eng. Jr. Med.*, 1945, ccxxxii, 617.
- b. RAPOPORT, S., and GUEST, G. M.: Effect of salicylates on the electrolyte structure of the blood plasma. I. Respiratory alkalosis in monkeys and dogs after sodium and methyl salicylate: the influence of hypnotic drugs and sodium bicarbonate on salicylate poisoning, *Jr. Clin. Invest.*, 1945, xxiv, 757.

2. ENGEL, G. L., ROMANO, J., FERRIS, E. B., JR., WEBB, J. P., and STEVENS, C. D.: A simple method of determining frequency spectrums in the electroencephalogram. Observations of effects of physiologic variation in dextrose, oxygen, posture, and acid-base balance on the normal E.E.G., *Arch. Neurol. and Psychiat.*, 1944, li, 134.
3. ENGEL, G. L., WEBB, J. P., and FERRIS, E. B., JR.: Quantitative electroencephalographic studies of anoxia in humans: comparison with acute alcoholic intoxication and hypoglycemia, *Jr. Clin. Invest.*, 1945, xxiv, 697.
4. ENGEL, G. L., FERRIS, E. B., JR., RAPOPORT, S., STEVENS, C. D., and LOGAN, M.: Hyperventilation. II. The relation between changes in electroencephalographic mean frequency and arterial and jugular blood; simultaneous study of venous blood of varying cranial origins. To be published.
5. FERRIS, E. B., STEVENS, C. D., WEBB, J. P., and ENGEL, G. L.: Voluntary breathholding. III. The relation of the maximum time of breathholding to the oxygen and carbon dioxide tensions of arterial blood, *Jr. Clin. Invest.*, 1946, xxv, 734.
6. DAVIS, H., and DAVIS, P.: The electrical activity of the brain: its relation to physiological states and to states of impaired consciousness, *Assoc. Res. Nerv. and Mental Dis. Proc.*, 1939, xix, 50.
- 7a. ROMANO, J., and ENGEL, G. L.: Delirium: I. E.E.G. data, *Arch. Neurol. and Psychiat.*, 1944, li, 356.
- b. ENGEL, G. L., and ROMANO, J.: Delirium: II. Reversibility of the E.E.G. with experimental procedures, *Arch. Neurol. and Psychiat.*, 1944, li, 378.
- c. ENGEL, G. L., and ROSENBAUM, M.: Delirium: III. E.E.G. changes associated with acute alcoholic intoxication, *Arch. Neurol. and Psychiat.*, 1945, liii, 44.
8. GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G.: Electroencephalographic response to overventilation and its relation to age, *Jr. Pediat.*, 1943, xxiii, 497.
- 9a. ENGEL, G. L., and MARGOLIN, S.: Clinical correlation of the electroencephalogram with carbohydrate metabolism, *Arch. Neurol. and Psychiat.*, 1941, xlv, 890.
- b. DAVIS, H., and WALLACE, W. McL.: Factors affecting changes produced in electroencephalogram by standardized hyperventilation, *Arch. Neurol. and Psychiat.*, 1942, xlvii, 606.
- c. RUBIN, M. A., and TURNER, E.: Blood sugar level and influence of hyperventilation on slow activity in E.E.G., *Proc. Soc. Exper. Biol. and Med.*, 1942, 1, 270.
- d. ENGEL, G. L., ROMANO, J., FERRIS, E. B., WEBB, J. P., and STEVENS, C. D.: (see reference 2).
- e. BRAZIER, M. A. B., FINESINGER, J. E., and SCHWAB, R. S.: Characteristics of the normal E.E.G. III. The effect of varying blood sugar levels on the occipital cortical potentials in adults during hyperventilation, *Jr. Clin. Invest.*, 1944, xxiii, 319.
- f. HEPPENSTALL, M.: The relation between the effects of the blood sugar level and hyperventilation on the electroencephalogram, *Jr. Neurol., Neurosurg. and Psychiat.*, 1944, i, 112.
10. HILL, L., and FLACK, M.: The influence of oxygen inhalation on muscular work, *Jr. Physiol.*, 1910, xl, 347.
11. DARROW, C. S., and PATHMAN, J. H.: Relation of heart rate to slow waves in the electroencephalogram during hyperventilation, *Am. Jr. Physiol.*, 1944, cxi, 583.
12. SCHWAB, R. S., in discussion of paper by DAVIS, H., and WALLACE, W. McL.: Factors affecting changes produced in electroencephalogram by standardized hyperventilation, *Arch. Neurol. and Psychiat.*, 1942, xlvii, 606.
- 13a. ARING, C. D., RYDER, H. W., ROSEMAN, E., ROSENBAUM, M., and FERRIS, E. B.: Effect of nicotinic acid and related substances on the intracranial blood flow of man, *Arch. Neurol. and Psychiat.*, 1941, xlv, 649.
- b. GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G.: The cerebral blood flow in man as influenced by adrenalin, caffeine, amyl nitrite, and histamine, *Am. Heart Jr.*, 1935, x, 916.



- 14a. DONOVAN, D. H.: The hyperventilation syndrome, *Irish Med. Jr.*, 1943, 519.
- b. SCHULTZER, P., and LEBEL, H.: Spontaneous hyperventilation tetany, *Acta med. Scandinav.*, 1939, ci, 303.
- c. FRASER, R., and SARGENT, W.: Hyperventilation attacks, *Brit. Med. Jr.*, 1938, i, 378.
- 15a. ENGEL, G. L., ROMANO, J., and McLIN, T. R.: Vasodepressor and carotid sinus syncope. Clinical, electroencephalographic and electrocardiographic observations, *Arch. Int. Med.*, 1944, lxxiv, 100.
- b. ENGEL, G. L.: Mechanisms of fainting, *Jr. Mt. Sinai Hosp.*, 1945, xii, 170.
16. ROMANO, J., and ENGEL, G. L.: Studies of syncope. III. Differentiation between vasodepressor and hysterical fainting, *Psychosom. Med.*, 1945, vii, 3.
17. HARVEY, A. M., and LILIENTHAL, J. L., JR.: Observations on the nature of tetany; the effect of adrenaline, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 163.
18. ROMANO, J., and ROSENBAUM, M.: Unpublished observations.
19. FENN, W. O., RAHN, H., OTIS, A. B., CHADWICK, L. E., EPSTEIN, M. A., HODG, M., HUNTER, S. W., and HOLMES, I. L. 1945. Personal communication.
20. OTIS, A., RAHN, H., EPSTEIN, M., and FENN, W. O.: Performance as related to composition of alveolar air, *Fed. Proc.*, 1946, v, 77.

# A SURVEY OF RECENT DEVELOPMENTS CONCERNING THE CONCEPTS OF CORONARY DISEASE AND ITS MANAGEMENT\*

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CORONARY disease is one of the most important diseases afflicting mankind. As the medical profession has reduced infantile mortality, improved sanitation, developed antibiotics and learned to deal with epidemic diseases, there has been a constant shift towards an increase in the frequency of degenerative diseases, like hypertension, arteriosclerosis, cancer, and their sequelae. Arteriosclerosis is thus becoming an ever growing problem and it will continue to grow in importance as the population becomes older. Arteriosclerosis is not a matter of aging, though it is more common in the elderly. It is a disease which affects not only old people, but also middle aged people and even young people. The concept that arteriosclerosis is a disease process and not just aging should ultimately prove fruitful in advancing our knowledge.

Arteriosclerosis can cause disease in all parts of the body, but the statistically important forms, as far as serious consequences are concerned, are nephrosclerosis, cerebral arteriosclerosis and coronary arteriosclerosis. It is fair to say that one out of every two persons in this audience will, unless something specific is found in the interim, succumb to coronary disease. Not only is this true of the medical profession but it is likewise true of other professions and of the executives, the people upon whose intelligence the welfare of this country depends to a large extent. We do not know why it is that the male suffers more ill effects from arteriosclerosis than does the female, nor why the "brain truster" in the broadest sense withstands this disease so much less than the average male population. Some day the answers will come. Apparently one of the prices paid by an individual for becoming a professional or executive type is that his chances of succumbing to coronary disease are greatly enhanced.

The fundamental cause of arteriosclerosis is poorly understood and the specific methods available to prevent or even to retard its development are practically nonexistent. This is one of the most important basic problems in medicine. The experimental work in the field of arteriosclerosis is clear in showing that cholesterol is involved in its development and that the feeding of cholesterol with the accompanying hypercholesterolemia induces atherosclerosis in the herbivorous rabbit and the omnivorous chicken, and that, when supplemented by thiouracil, it apparently can also induce this

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lesion in the dog. Experimental evidence also supports the idea that strain upon the circulation facilitates its development. It appears also that thyroid secretion and potassium iodide tend to retard it, while hypothyroidism tends to favor its development. Other factors involved in the process of experimental atherosclerosis are still controversial. In the present state of our knowledge it is not yet justified to advocate a cholesterol-poor diet in man in the hope of retarding atherosclerosis because there is reason to believe that endogenous cholesterol produced even on a cholesterol-poor diet may still lead to atherosclerosis. Recent experience in animals has suggested the possibility that macromolecular substances lead to blood vessel plaques and it may be that cholesterol operates as a macromolecular substance. Some inconclusive experiences suggest that ischemia or anoxemia of the vascular wall, which is normally richly supplied by vasa vasorum, contributes to the development of atherosclerosis. These are the problems for the future. For the present these concepts cannot yet be employed in the clinical handling of arteriosclerosis.

When we speak of coronary disease we speak statistically primarily of coronary atherosclerosis and its sequelae. However, the coronary blood vessels are subject to other diseases, such as periarteritis nodosa, thromboangiitis obliterans and other less clearly defined vascular diseases. Emboli, usually from preëxisting thrombi but also of material from valve vegetations, especially in subacute bacterial endocarditis, also lodge in the coronary arteries. Rheumatic coronary endarteritis is said to occur. Syphilitic closure of the coronary ostia is common. Invasion of the coronary vessels by cancerous growth and traumatic damage to the coronary vessels are observed. I mention these other causes simply to reëmphasize that atherosclerosis, while the most important single cause of coronary disease, is not the sole cause.

Coronary sclerosis leads to ill effects by handicapping the adjustments of the coronary vessels to the needs of the heart for varying amounts of blood flow. The rigidity of these vessels which is an accompaniment of coronary sclerosis makes them less distensible and hence more poorly adapted for wide variation of blood flow such as is required to meet the ordinary and extraordinary demands put upon the heart. While coronary sclerosis tends to develop in discrete locations, rather than diffusely, this interference with distensibility is still a serious consequence. Sclerosis of a coronary vessel also leads to narrowing of the lumen and thus interferes with the blood flow to the region which it supplies.

There are compensatory blood channels, namely the intercoronary communications, arteriovenous anastomoses, Thebesian vessels and extra-cardiac collaterals, which enlarge and take over the supply of blood to the region whose coronary artery is occluded or narrowed. The adequacy of this auxiliary blood supply depends most of all upon the rapidity of the narrowing of the coronary arteries. Age is also of some importance because the

coronary arteries are more nearly end arteries functionally in the young than in the old in whom these auxiliary channels have had time to develop. Clinically this is demonstrated by the fact that closure of a single coronary vessel is apt to lead to infarction in a young individual whereas in an older person closure of more than one vessel supplying a region is ordinarily required before infarction occurs. The rôle of the Thebesian vessels is shown by the fact that infarction of the lateral wall of the right ventricle occurs only once in every 40 cases. This is so because it has been demonstrated that 90 to 95 per cent of the Thebesian vessels open into the right heart. In the left heart where infarcts are more prevalent the Thebesian drainage constitutes at most 5 to 10 per cent. Personally, I believe that the infarcts of the lateral wall of the right ventricle arise by virtue of the endocardial thromboses which plug up the openings of the Thebesian vessels. The rôle of the extra-cardiac collaterals is clearly revealed by the occasional finding at necropsy of almost complete syphilitic closure of both coronary ostia with little or no disability on the part of the patient for many years until a few months before the rapid downward course leading to death. Thus, in understanding the ill effects of coronary disease account must be taken not only of the coronary abnormalities themselves but also of the manner and completeness of the compensatory secondary circulation which can take over the task of feeding the impoverished areas of the heart.

An examination of the architecture of the coronary vessels at necropsy as ordinarily performed by the traditional pathologist fails to reveal the nature of collateral circulation. It also fails to determine the state of the smaller arteries and the arterioles. The presence of a plaque need not indicate narrowing of the lumen since in several instances experimental distention of the involved coronary artery with a pressure of the order existing in life has revealed aneurysmal dilatation at this point. The practice of injecting the coronary system in necropsy examinations should be more widespread. For these and other reasons, examination of the coronary vessels at necropsy often fails to provide sufficient evidence from which the clinical course of the patient can be reconstructed. This is not surprising since an examination of the water and sewage system of a municipality confined to an examination of the pipes is inadequate to reconstruct the ability of the system to provide water and to remove sewage. It is obvious that the pumps and the other factors involved must be examined in arriving at a complete analysis. This is true also of the coronary system. Other factors besides the architecture of the coronary vessels are involved in determining the adequacy of coronary flow. A dynamic viewpoint which takes into account all the factors must be employed therefore in analyzing coronary disease for clinical purposes. The functional state of the coronary vessels and the dynamics of the coronary flow must be evaluated. It is for this reason that the term coronary insufficiency to express an inadequate coronary flow has been created and gained wide vogue recently. This dynamic or physio-

logical concept serves a useful purpose in that it permits the clinician to judge whether the coronary system is able to nourish the heart adequately.

Coronary insufficiency from the clinical standpoint involves two factors. One is the absolute rate of coronary flow, the other is the need, per unit of time, for coronary blood flow to maintain the heart in the status quo. Even in the normal heart excessive exertion may so increase the need for coronary blood flow that the compensatory mechanisms available to increase the normal coronary circulation may fail and coronary insufficiency may ensue. Coronary insufficiency therefore is really to be expressed in terms of relative insufficiency. It arises whenever the coronary blood flow can not keep up with the needs for it. This may be due either to an increase in the need or to a reduction in the supply.

Coronary insufficiency may be focal, involving only a portion of the heart, or it may be generalized, involving the entire heart. Focal coronary insufficiency is more apt to lead to pain of cardiac origin and to confluent myocardial infarction while generalized coronary insufficiency is more apt to lead to chronic or acute heart failure. Obviously exceptions occur.

Coronary insufficiency can be subdivided also according to the time of its duration. Thus, transitory coronary insufficiency, which is the cause of anginal attacks, acute heart failure, paroxysmal dyspnea and acute pulmonary edema, lasts for a matter of minutes or an hour or so. It may be terminal, of course, ordinarily by leading to ectopic rhythms arising in the ischemic area which terminate in ventricular fibrillation.

Coronary insufficiency may be more protracted and lead to myocardial infarction.

Coronary insufficiency may be chronic. Many patients with a healed myocardial infarct may go into this chronic state. Two varieties of chronic coronary insufficiency exist. The first is benign. The symptoms and signs of the coronary insufficiency progress very little over months and years apparently because the compensatory collateral circulation can make up for the primary defects. The second variety is more malignant. Here the primary defect progresses inexorably faster than the compensatory mechanisms can keep up with it, with the result that the signs and symptoms progress continuously, and sometimes at an accelerating rate, until death. Of course, the transitory and the protracted forms of coronary insufficiency are often superimposed upon the chronic coronary insufficiency and may be the terminal event.

Coronary insufficiency, therefore, is primarily a chronic disease of benign or malignant character. More attention needs to be paid to this aspect of coronary disease despite the lure to concentrate on the more dramatic episodes of transitory coronary insufficiency and acute myocardial infarction. We need to consider coronary disease as a long term problem and to concern ourselves with this aspect of it more than we have in the past. Of course, this does not mean that we should pay less attention to the acute varieties.

In order that we may understand the rationale of prognosis and management of coronary insufficiency we must be aware (1) of the natural history of coronary disease and (2) of the factors involved in the control of the coronary circulation.

In considering the control of the coronary circulation too much attention has been directed in the past to the effects of change in caliber of the coronary vessels due to its musculature and not enough to the other factors involved. Coronary insufficiency, I believe, occurs more often by virtue of disturbances of the dynamics of coronary flow and to anatomic narrowing and obstruction of the coronary lumina than to coronary vasoconstriction or spasm. In fact, I would hazard the guess that coronary spasm is a rare occurrence and coronary vasoconstriction is relatively infrequent. This is not to be taken to mean that coronary vasodilator drugs are ineffective, but their rôle is to supplement coronary flow rather than to relieve vasoconstriction.

In considering the control of the coronary flow, it must first be pointed out that the coronary vessels are to a large extent enclosed within the walls of the heart chambers which undergo changes in tension during the heart cycle. In the case of the right ventricle, the cyclic change is of the order of 50 mm. of mercury, and in the case of the left ventricle it is of the order of 180 mm. of mercury. As these pressures rise in systole they exert a squeeze upon the coronary vessels which tends to narrow them and cause a systolic retardation in flow. Actually the situation is more complex. Thus it has been shown that the subendocardial layers of the ventricles are the only ones in which this magnitude of squeeze takes place. In the subepicardial regions the pressure actually remains around zero during the heart cycle. In short, the squeeze due to the systole of the ventricles applies only to subendocardial layers and lessens across the thickness of the ventricular wall until at the epicardium it is practically absent. This is the reason that focal necrosis, the anatomical sign, of transitory coronary insufficiency, is more prevalent beneath the endocardium.

Far more important is the fact that the coronary blood flow is dependent upon the fluctuations in pressure at the root of the aorta which is the driving force for the coronary flow. Since the aortic pressure is higher in systole, it would appear that, except only in the subendocardial layers of the left ventricle, there is normally a systolic accentuation of coronary flow. Furthermore, it is possible that under abnormal conditions, such as strain of the right heart, the systolic rise in wall tension in the right heart may be greater than the systolic rise in aortic pressure, leading to a systolic slowing of the coronary circulation in this part of the heart.

Since 90 to 95 per cent of the coronary drainage is into the right heart it follows that acute engorgement of the right heart such as occurs in recent pulmonary embolism and acute congestive right heart failure will impede coronary flow and lead per se to coronary insufficiency. This is particularly striking since at the same time the need for coronary blood flow in the right

heart is increased because the work of the right heart increases. A similar effect though less striking may occur in chronic congestive right heart failure.

Recently we have demonstrated in animal experiments that the coronary flow is a direct function of the cardiac output. The blood propelled by the left ventricle is distributed between the coronary vessels and the rest of the systemic circulation and both of these tend to fluctuate in the same direction as the output of the heart. This is an important mechanical regulation of coronary flow according to the need for it. This adjustment of coronary flow to cardiac output may occur with little or no rise in blood pressure. The clinician should be aware of this, since otherwise he would be hard put to explain how the coronary flow increases in cases of exercise, anemia and hyperthyroidism in which the blood pressure may be changed very little, if at all. Arteriosclerosis of the coronary vessels with their resulting rigidity permits the development of coronary insufficiency when the heart pumps more blood per minute, since the rigidity of the coronary vessels prevents the beautiful mechanical adaptation of coronary flow to cardiac output present in uninvolved coronary vessels.

Another thing that is lost sight of is that the coronary circuit is only one of many in parallel in the systemic circulation. Hence, vasodilatation or vasoconstriction of other paths of the systemic circulation, notably the splanchnic area, will divert some of the blood pumped out by the left ventricle away from or into the coronary circulation. Ordinarily this is accompanied by a blood pressure fall or rise, but in animal experiments we have seen this occur without significant change in blood pressure. We attribute this lack of blood pressure change to the fact that the diverted blood mechanically alters the caliber of the coronary bed so that the resistance to flow over the coronary circuit is sometimes affected to the same extent as, but in the opposite direction to, that in the other systemic circulatory beds. It is easy to conceive of mild adjustments in the caliber of the extracoronary systemic beds occurring clinically and resulting in diversion of blood to or away from the coronary circulation without a noticeable change in blood pressure. In fact, some of the drugs which are employed to dilate the coronary vessels may defeat the purpose for which they are used by virtue of their having a greater dilatory effect on other systemic circuits; and this may happen without their appreciably changing the blood pressure.

The caliber of the coronary vessels can be changed by vasomotor influences. Our own experience, contrary to those of others, has shown that the vagi are coronary dilators and not coronary constrictors. This is a cholinergic effect since the vagal coronary dilation is prevented by the exhibition of atropine. The sympathetic nerves, when their effect on cardiac work and metabolism is eliminated, cause both a vasodilatation and a vasoconstriction of the coronary circuit. The sympathetic vasoconstriction is the more powerful and is adrenergic since it can be abolished by ergotamine

and the dioxane derivative, F933. These nervous influences are constantly active, as we have shown, but they are not powerful. They are as weak as the influence of nerves in controlling cerebral and pulmonary blood vessel caliber. Vasoconstriction of neurogenic origin; on this basis, must be sympathetic in nature and not vagal. Our own experiments have failed to show a vagal vasoconstriction of the coronary vessels and are opposed to the so-called vagal pulmono-coronary vasoconstriction reflex. Atropine if it has any benefits in myocardial infarction and in pulmonary embolism must operate in other ways than the supposed abolition of vagal coronary vasoconstriction.

When we eliminated all these extraneous effects in our animal experiments, we found that most drugs are coronary dilators. Among the most powerful are the nitrites and papaverine. The xanthines are much weaker and would appear to be ineffective when given by mouth. Acetylcholine and mecholyl are coronary dilators and their effect is abolished by atropine. Morphine, quinidine, calcium and sodium are coronary dilators and so is potassium in small doses. Potassium in large doses, however, is a powerful vasoconstrictor, leading to real coronary spasm. Pitressin, too is a powerful coronary vasoconstrictor, and so is foreign species blood. Adrenalin is a strong coronary dilator. Its ineffectiveness clinically as a coronary dilator is due to the fact that its side actions lead to an increased need for coronary blood flow far in excess of its dilator effect, with the net result that a relative coronary insufficiency develops. This illustrates that the determination of a vasodilating action of a drug does not per se indicate its utility in coronary insufficiency. Obviously adrenalin is not to be used as a coronary dilator clinically. In fact, it has been used as a method of bringing about coronary insufficiency as a clinical test for coronary disease. This illustrates that data obtained from animal experimentation can not be taken as applicable in clinical disease without first checking by clinical tests. Animal experimentation tells what can happen under controlled conditions but does not necessarily tell what does happen in the diseased patient. The latter belongs to the discipline of clinical research.

The story of the control of the coronary circulation would not be complete without mention of the final adjusting mechanism which depends upon unknown vasodilator substances which appear whenever relative ischemia or anoxemia of the heart occurs. It has been clearly shown that a lessening of the oxygen content of the arterial blood leads to coronary vasodilation and we have shown that temporary occlusion of a coronary vessel is followed, as in the case of other systemic circuits, by a powerful reactive hyperemia. This implies that there is a final adjusting mechanism which regulates the caliber of the coronary vessel to need. The development of anoxemia or ischemia, which ensues when compensatory mechanisms fail, tends to produce vasodilator substances which adapt the coronary flow to the needs at the moment. Obviously when the maladjustment is great even this final adjustment fails and relative coronary insufficiency results.



My purpose in this long digression on the control of the coronary circulation has been to bring you up to date on the complexity of the factors involved in regulating the blood supply to the heart and to make you ask yourself critically whether many of the glib explanations prevalent in current clinical thinking are really true or not. The first step in the rational approach to therapy and management of coronary disease is to remove taboos and fads which tend to creep in to any field of medicine as a result of its authoritative development. It is for a similar reason that I would like to discuss the mechanism of cardiac pain.

Of course, you know that not all chest pain is cardiac in origin. Many processes tend to imitate angina pectoris and these must first be excluded in every case where any doubt exists. It is notorious that the symptomatology of coronary disease is elusive. That is one of the reasons why electrocardiography has lately gained such vogue, but even here there is a tendency to read too much into the electrocardiogram and I would not be rash in stating that all of us have erroneously diagnosed many cases of chest pain as of cardiac origin. The interpretation of the electrocardiogram is subjective and as prone to errors as any other clinical method of diagnosis. We all know that a normal electrocardiogram does not necessarily exclude coronary disease. It is becoming clearer also that many other diseases can lead to electrocardiographic distortions which are imitative of coronary patterns. A need has developed for some tests to measure the adequacy of the coronary circulation.

Two such tests are now in vogue. One is the anoxemia test which I consider too hazardous for widespread use, even though its advocates point out that the administration of oxygen will quickly alleviate its untoward effects. The other is the exercise tolerance test with which we have recently gained some experience. This test depends upon quantitative exercise with the Master stairs and the observation of the electrocardiographic changes induced by it immediately after exercise and over the next 10 minutes. This test must be performed carefully, it is to be used only when the electrocardiogram is normal or at most shows non-specific abnormalities. It should be carried out only by a trained physician who has been instructed in its methodology. It should be stopped whenever pain, fatigue, or shortness of breath begin to appear. It has been the experience of those who have used this test that it will bring out positive evidence of coronary disease in a number of occult or otherwise doubtful instances. In this way it is of value in the clinical assay of a case suspected of chronic coronary insufficiency. Unfortunately the positive results occur in only a small percentage of cases so that a negative test does not exclude coronary insufficiency. In our hands, false positive tests have not as yet occurred. The changes we believe should not be dealt with quantitatively, but the interpretation should depend upon changes in the final segment, the S-T-T complex, similar to those encountered during a spontaneous attack of transitory coronary insufficiency.

Time does not permit me to analyze these electrocardiographic changes in detail. Nor is there time to consider the routine electrocardiogram of coronary insufficiency.

Angina pectoris implies the appearance of pain. The physiology of sensation is therefore applicable. This involves the determination of the pain stimulus, the location of the pain endings in the heart, the paths pursued by the pain fibers, the psycho-physiology of pain appreciation and the general physiology of referred pain.

The evidence is fairly complete that the pain substance giving rise to cardiac pain is a diffusible material which can pass in and out the blood stream readily. It is non-volatile in the sense that it can pass unchanged through the lung circulation. It is formed during ischemia of heart muscle and is destroyed in the presence of an adequate blood supply. It is not clear whether it is an acid metabolite like lactic acid, phosphoric acid, pyruvic acid or succinic acid, or is a non-acid metabolite like histamine, phosphocreatine, adenosine or potassium. It appears that it can be manufactured by ischemic skeletal muscle as well as by heart muscle and this is important since the skeletal musculature constitutes half the body mass. Because the stimulation involves end organs, the substance must accumulate in quantities above a threshold in order to stimulate the pain endings. This means that in the absence of pain, the pain-producing material need not be absent but may be at any level below the threshold. Obviously, therefore, the amount of further accumulation of pain-producing material may be variable since at one extreme there may be none of this material present beforehand and, at the other extreme, it may have already accumulated to just below the threshold level.

The pain endings in the heart, aside from those in the parietal pericardium, appear to be located only in and around the coronary vessels. It is there that the pain-producing substance must accumulate. Experience has shown that the epicardium, endocardium and myocardium are free of pain endings. The pain fibers are located in the adventitia of the coronary vessels and travel up to form a plexus around the mouths of the coronary arteries. There they are joined by pain fibers coming from the root of the aorta and others from the great vessels as well as those from the parietal pericardium. The pain fibers join the cardiac plexuses in the mediastinum and travel to the spinal cord and medulla via the sympathetic chain and the vagi, and eventually reach that part of the cortex where the sensorium is located. Pain fibers and other fibers from somatic regions of the same segmental area join these visceral pain fibers at various levels so that at the sensorium there is a final common terminal for these visceral and more commonly experienced somatic sensations.

The pain endings of the heart, like other end organs of sensation, may vary in the level of their threshold, that is they may require more or less of the pain producing substance to stimulate them under different circum-

stances. This variability may result from coronary disease. Mild degrees of ischemia may make the end organs more sensitive; greater degrees may dull them and even destroy them. Disease may also affect the pain pathways of the heart. Since arteriosclerosis involves the vasa vasorum nourishing the adventitia of the coronary vessels it is possible that the disease process may irritate these fibers and so lead to stimuli engendered at these irritable foci rather than at the nerve endings themselves. More advanced disease may inhibit the transmission of nerve impulses over these pain fibers and may even destroy them. This is another variable in the development of pain sensations from the heart.

People vary greatly in their ability to appreciate painful stimuli. There are hypo- and hyper-sensitive persons as far as pain is concerned. This too introduces an element of variability. It is quite likely that conditioning plays an important rôle in making the pain sensation obtained more readily appreciated. It would appear that the more often painful stimuli occur, the more often angina will develop, that is, the more readily pain can be appreciated. It follows, therefore, that any procedure that will keep a patient free from anginal attacks will, as it were, uncondition him and make it harder for anginal pain to recur.

One of the peculiarities which heart pain shares with all referred pain is that it is referred to somatic areas from which the person is more accustomed to perceive sensation than from the heart. This you are all aware of by virtue of the classical and less common somatic distribution of pain of cardiac origin. It would take us too far afield to enter into the matter of referred pain. However, I wish to stress that irritation in the aorta, in other visceral organs and in somatic areas may make anginal pain appear more easily. Impulses coming from somatic areas may summate in the final common terminal with those from the heart and so require less pain stimulation of the heart to give rise to the sensation of cardiac pain. We have been able to show that exercising the left hand in patients susceptible to angina, while the blood supply to the hand is cut off by a blood pressure cuff, can often induce a typical minor anginal syndrome. Apparently the painful stimulation from the hand summates with the sub-threshold stimulation of the heart so that the two together can be appreciated by the sensorium as pain.

These few remarks on the pathogenesis of pain should orient the clinician in his interpretation of the meaning of this sensation. He should appreciate that just because cardiac pain is a threshold phenomenon, the appearance of pain will come on and wax briskly since the heart is constantly beating. This does not imply that angina is due to coronary spasm. Any circumstance which causes a rapid accumulation of pain-producing substances will lead suddenly to the appearance of pain. This concept of angina pectoris will help the clinician to explain the otherwise inexplicable lack of relationship of anginal pain to effort, why sometimes little effort leads to pain and

at other times in the same patient much greater effort does not. It is the state of the nervous system and the rate of accumulation and disposal of the pain-producing material that accounts for this variability.

There is one other matter I would like to discuss briefly and that is the difference in effect on the heart of a short and prolonged period of ischemia. The difference in effect between a transitory and a protracted period of coronary insufficiency is a matter of degree and a matter of reversibility. For example, it can be shown that when a coronary artery is occluded the region supplied no longer contracts but bulges during systole. If the occlusion is released at the end of a minute or so the power to contract once again develops, but if the occlusion is kept up for several minutes the change is irreversible. Similarly, on occluding a coronary artery the region supplied will show a decline in the content of glycogen, phosphocreatine and other chemical precursors of contraction. At the same time phosphoric acid, lactic acid, pyruvic acid and succinic acid increase. If the coronary artery is released at the end of a minute or so these changes are reversed but if the occlusion is released after five or more minutes the change becomes irreversible. A similar difference between a minute and several minutes of occlusion can be demonstrated for the development of acidity in the ischemic area. It has further been demonstrated that if animals are taken and the coronary arteries temporarily occluded for five minutes and then the chest closed and the pneumothorax relieved, that a series of electrocardiographic changes develop such as are encountered following myocardial infarction. This is true also if the experiment is repeated in other dogs but the occlusion kept on for 15 or more minutes. However, when these animals are sacrificed later it is found that the shorter occlusion had not led to histologically recognizable infarction while the latter had. These experiences show that occlusion operates at first in a reversible fashion and only when it is prolonged do the effects become irreversible and capable of histological demonstration. Thus, histo-biochemical changes precede histo-anatomical ones. It is fair to state that the local effects of ischemia are related to the product of the severity and the duration of the ischemia.

I am sure that by this time you have begun to ask yourselves how these fundamental problems help in the diagnosis, prognosis and management of coronary disease. As for diagnosis, what I have said shows why history alone may often be misleading, why there is need for objective tests. Much remains to be done in this field, but with the consideration and exclusion of other causes of these symptoms, with the aid of properly analyzed electrocardiograms, and with such procedures as the exercise test, the diagnosis of coronary disease may become more precise.

As to prognosis, it is obvious that the clinician must become familiar with the average development in coronary disease. He must recognize that about one-fifth of the cases of recent myocardial infarction die during their hospital stay; that the average expectancy of life, following an infarct is five

years, but that the scatter is quite large. We have seen cases who have lived very comfortably for over 20 years following an infarction. We are all aware of the fact that the factors which determine the prognosis in recent myocardial infarction and in other forms of coronary disease are still too poorly understood for us to be able to prognosticate accurately in a given patient. It is true that those people who develop a marked drop in blood pressure or go into shock have a poor prognosis. It is true that the development of congestive heart failure carries with it a serious outlook. It is true that the presence of diabetes adds to the gravity of the outlook. Nevertheless we do not know how to prognosticate precisely how long a given patient with coronary disease will live. It is therefore unwise to give a poor prognosis. Too many patients with coronary disease are frightened unnecessarily by their physicians and many who otherwise might lead a useful and happy existence are made miserable and useless by an unjustified poor prognosis.

Of course, the patient should have his affairs in order, should be moderate in his undertakings, should learn how to play as well as how to slow up in his work, how to cut down and avoid peak loads, how to develop a carefree attitude, how to keep his weight down to normal—in short, he should learn how to live. But to take him away entirely from his life's occupation, to let him live on disability insurance, is in most cases unnecessary and even harmful. Ninety-five per cent of all coronary fatalities appear to occur without precipitating cause, many occur during bed rest or sleep. In our present state of knowledge we know too little of how to prevent the further progress of atherosclerosis and its sequelae to warrant prohibitions.

When coronary disease was first recognized, myocardial infarction was a necropsy diagnosis so that the impression arose that it was inevitably fatal. As our knowledge grew and it became clinically recognizable, infarction became less ominous. Today we know that many people have had infarcts without any symptoms, without any special medical care and the knowledge of this was written in their hearts and revealed at necropsy some time later when they died of some other circumstance or of a new infarction. I have seen the hearts of some of these people who have worked in hospitals or in close association with doctors and who had their infarction without enough symptoms to warrant their consulting the readily accessible physicians. I have seen this too in the hearts of doctors. You are all aware of the fact that before we became coronary conscious, many people had indigestion as a sole manifestation of their coronary episode. In short, coronary disease is more prevalent than we realized and even infarction is statistically more benign than we appreciated.

I would like to emphasize that I consider myocardial infarction a self-limited disease, a process which by the time the clinician sees the case is ordinarily already a matter of convalescence, that four out of five patients will survive the episode, and that most of them will have little if any handicap.

Some of course will develop chronic coronary insufficiency, but others will be completely restored and have, at most, only the psychological fear that all lay people and too many physicians attach to coronary episodes. I think all of us should practice the psychology of hope. There has been too much of the psychology of fear.

As already hinted the primary management problem in coronary disease is to deal with chronic coronary insufficiency. This is a problem involving more than medication. It is a problem in which the physician has to survey with his patient the entire mode of his existence and to try to create a proper philosophy of living. This should be adapted to the temperament of the patient. The fearful one will have to be reassured, the domineering one will have to be taken down a peg or so. It is in this field that a sympathetic approach, the spending of sufficient time to delve into the patient's problems and the constant repetition of the theme of proper living at different visits will repay the effort involved. It is here that the physician can practice the true art of medicine. It is my view that mismanagement arises from the lack of time spent with a patient in going over all aspects of his activities. Since we know of no real way of retarding arteriosclerosis and since we know of no way of predicting when the next coronary attack will come nor whether or not it will be fatal, we should view with grave suspicion any tendencies on our part to impose on him undue prohibitions.

It is the experience of all that undue exertion and undue emotion may precipitate angina and even a myocardial infarct. The particular circumstances that seem to act as trigger mechanisms for angina should be thoroughly explored in each case and ways devised to avoid them.

Many times the trigger mechanism involved in angina is paroxysmal tachycardia, paroxysmal auricular fibrillation or flutter, and, even more commonly, frequent premature systoles. It is for this reason that quinidine has proved so valuable prophylactically. Quinidine is perhaps the best "soothing" agent for ectopic rhythms. It is therefore one of the best drugs available prophylactically in chronic coronary disease complicated by ectopic rhythms. Papaverine works in a similar fashion on ventricular ectopic rhythms; in addition, it is a sedative which is not habit forming and it is a powerful coronary vasodilator. It too, like quinidine, should be employed more often prophylactically than it has been. Xanthines, on the contrary, are used far too often. Of all the xanthines, the only one that appears to work by mouth in my experience, is theocalcin, and this I attribute to the calcium. Xanthines are ordinarily combined with a barbiturate and the barbiturate of the combination is the effective agent. Barbiturates are used alone for sedation and as hypnotics.

Tobacco should be discouraged in coronary disease. It leads to vascular narrowing, presumably including the coronary vessels. Alcohol on the contrary should be encouraged. Port wine is a good hypnotic. A cocktail or two can make many people see life in a more pleasant manner and helps

them to relax. Wines with meals should be encouraged. Alcohol leads to dilatation of blood vessels and presumably this affects the coronary arteries as well. I find that permission by the physician for the patient to indulge in alcohol makes other restraints more tolerable. As to diet the key is moderation. There is no specific food which needs to be avoided. The patient, however, should reduce his weight when he is overweight. When the "coronary" patient has diabetes, the diabetes should be treated moderately. We have found that rigid control of the diabetes actually leads to more frequent anginal attacks and when the control is less rigid the patients do better.

Rest is an important item in management. Some people do well when they are encouraged to take a rest period (or even a nap) during the day. It breaks the tension under which the high powered executive lives. Frequent excursions and holidays are in order. The patient should undertake to keep himself fit by a program of graded exercise. This may include walking, golf and similar activities. These should be indulged in up to the point of tolerance, that is short of the point of fatigue, pain or shortness of breath. Inactivity makes even the healthy person physically unfit. One cannot avoid peaks of exertion or emotional stress in the environment in which most of us live. This is true also of the patient with coronary disease who does not lead an entirely sheltered life, and most of them should not. It, therefore, behooves the patient to put himself in as good a physical condition as possible. When properly carried out, it is amazing how much improvement in physical capacity can be attained. In this program of graded exercise, caution should be used. A sense of competition even with his own par, should be avoided. Any competitive exercise, which tends to make individuals do more than they should, should be avoided. The patient should be encouraged to stop his effort when he feels he has had enough. Incidentally, a game of cards may, by its competitive character, be more harmful than a long walk or fishing!

The nitrites are extremely useful in coronary insufficiency. Nitroglycerine has stood up best of all. Patients soon learn how to help alleviate their anginal attacks with nitroglycerine under the tongue. Nitroglycerine, furthermore, may be employed prophylactically. It may be taken a half hour before an interview or other activity which the patient can not avoid and which he has found is apt to lead to anginal attack.

The handling of congestive heart failure complicating coronary disease is no different from the treatment of congestive failure of any origin and there are no contraindications to the use of digitalis or mercurial diuretics, provided there is an indication for their employment.

Status angiosus may require protracted bed rest. It is amazing how often a period of bed rest at home or in the hospital improves the condition of the patient for a period long after the rest has been completed. When rest is ineffective, alcohol injection of the left (or right) stellate ganglion may lead to remarkable alleviation of status angiosus. It does not remove all the

warning signals of overactivity. The patient should be taught to look for dyspnea, fatigue and other signs indicating that he is doing too much to replace his dependence on pain as a warning. Total thyroidectomy and the Beck operation have not come up to expectations and are rarely if ever justified for angina pectoris.

My dissertation would not be complete without some remarks on the management of recent myocardial infarction. First, I wish to stress that one should sharply distinguish between chronic coronary insufficiency, an anginal attack and an old healed infarct on the one hand, and a recent myocardial infarct on the other. This is true not only clinically but also in interpreting electrocardiograms. Too many men in reading an electrocardiogram showing coronary pattern, jump to the conclusion that this is evidence of a recent infarct and fail to check this deduction by taking serial curves, which tend to distinguish the recent myocardial infarct from other forms of coronary disease. The real abuse of bed rest is to put a patient to bed for six or more weeks when the evidence is not clearcut that he has a recent infarct.

Rest is still the best form of therapy for a recent myocardial infarction. The rest should be complete for two or three weeks and may have to be complete for up to six weeks. Even at rest the heart does work. If healing is to be facilitated one should not superimpose an additional load upon the heart which comes from incomplete bed rest. It may be necessary, when orthopnea is troublesome or when the patient is uncomfortable flat on his back, to raise the head of the bed or even to permit the patient to have his rest sitting in an easy chair. Likewise it may be necessary when a patient has difficulty in using a bed pan to permit him to use a commode at the bed side. The aim in treatment is not so much *bed* rest as the approach to complete and comfortable rest. After the period of complete bed rest the length of which is determined by the clinical evolution and the rate of healing revealed in the electrocardiogram, the patient is permitted gradually to sit up, to use a wheel chair and then to get up and about. He then should have a holiday of a month or more before being permitted to resume his normal activities with certain restrictions. The overall time before normal activities on a restricted scale can be resumed is variable, but ordinarily is a matter of three to six months at most.

Recently considerable discussion has arisen in regard to the abuse of rest in recent myocardial infarction because of the hazards of hypostatic pneumonia, bed sores, and venous thrombosis and pulmonary embolism. These are real hazards but not as frequent as some would have us believe. They are most apt to occur in debilitated and in elderly patients. Hypostatic pneumonia can be avoided by shifting the position of the patient from time to time. Voluntary deep breathing periodically also has been suggested as a preventive measure. Thromboembolic phenomena are a much more serious complication. Massage of the legs and their movement by the patient from



time to time may be employed to prevent thrombosis. Recently, anticoagulants in the form of dicumarol have been suggested for this purpose. While the results are not conclusive and a study devoted to the evaluation of dicumarol is now being pursued in a number of institutions under the auspices of the American Heart Association, sufficient evidence has accumulated to suggest that this method of therapy is effective. The number of thromboembolic phenomena and fatalities complicating myocardial infarction are sharply reduced by anticoagulant therapy when carried out under hospital management with a careful assay of prothrombin times during the course of treatment. It appears that there is a real likelihood that this will be a definite advance in the management of recent myocardial infarction. I would be prepared to state at the present time that any patient who shows a thromboembolic episode after a recent myocardial infarction deserves to be placed upon dicumarol therapy. It may turn out that every patient with a recent myocardial infarction should receive this form of therapy prophylactically, during the period of bed rest following infarction. However, the final decision on this latter point will have to await the final report of current studies.

Shock is one of the serious complications of recent myocardial infarction. It should be distinguished from the immediate vascular collapse which often accompanies infarction. Dr. Brams of our hospital, in some as yet unpublished studies, has found that desoxyephedrine, on several occasions, has had a remarkable effect in counteracting the vascular collapse of myocardial infarction. If further experience verifies this finding, it may become a useful addition to our armamentarium. Shock, following recent infarction, and by this I mean the same kind of syndrome which follows trauma and surgery, should be handled like shock of any other origin. Blood transfusions, administered at a rate slow enough to avoid burdening the heart, have been found useful in avoiding the irreversible stage and death. They should not be given when there is evidence of pulmonary edema or when the systemic venous pressure is elevated. When transfusions are given the patient should be carefully observed during administration to avoid evidences of pulmonary or systemic venous engorgement. Collapse and shock are serious complications and are apt to result in death of the patient, when untreated. The use of pressor drugs and of blood transfusions are heroic procedures to avoid these end results, and their employment is therefore a matter of weighing risks.

The appearance of paroxysmal rapid heart action requires treatment. Such rapid heart action is a burden on the already weakened infarcted heart. Paroxysmal auricular fibrillation can be treated with strophanthin intravenously. Paroxysmal auricular tachycardia and paroxysmal auricular flutter can be treated with quinidine. Frequent ventricular premature systoles occurring during the course of infarction require the employment of

quinidine, or of papaverine, or of both. Paroxysmal ventricular tachycardia requires heroic therapy, either oral quinidine or papaverine intravenously.

It is well recognized that morphine is an extremely useful drug in recent myocardial infarction. Occasionally demerol may be used in its place. Some people advocate the use of atropine, and this drug may be useful in preventing reflexogenic ectopic rhythms. I still believe that, even in the absence of ectopic rhythms, papaverine is a useful drug in recent myocardial infarction provided it is used in high enough doses. However, it must be pointed out that it appears to be ineffective in some cases and in others it leads to unpleasant side actions.

The question of oxygen therapy is constantly raised. It is indicated whenever pulmonary edema or pulmonary congestion is present. I am not so sure that it should be used in every case of recent myocardial infarction. Of course, it can do no harm except for the fact that to many patients it carries the implication that they are moribund. Some patients develop a sense of claustrophobia when they are placed in an oxygen tent. I believe that the nasal catheter is too irritating to be employed ordinarily; it often leads to irritation or inflammation of the pharynx which causes hacking and coughing, both undesirable efforts. Of all methods of administering oxygen, probably the best is the use of a mask such as was employed in the Air Forces in high altitude flying.

When diabetes complicates a recent myocardial infarction the proper use of insulin and sugar will avoid ketosis. The treatment, however, must not be aimed at making the patient sugar free. A little sugar spilled in the urine is not dangerous.

Congestive heart failure often complicates recent myocardial infarction and it should be handled exactly like congestive failure of any other cause. In fact, the use of mercurial diuretics and of digitalis should be vigorously pursued. Digitalis is not contraindicated in recent myocardial infarction. It does not lead to coronary constriction except in toxic doses, and it does not lead to rupture of the heart. Digitalis should be given to relieve the congestion and should be stopped or reduced when this effect is obtained or when toxic symptoms appear.

In this survey I have tried to cover only a few of the main points in recent concepts of coronary disease and its management. Obviously I have dealt with many a controversial aspect and have presented a number of matters which are still being investigated. I have not hesitated to express my own views, realizing full well that in many places I am not in accord with current beliefs and fads. I have done so because these are my convictions, based on a survey of the literature and personal experience in the laboratory and as an observer and experimenter at the bedside. In closing, I would like to emphasize once again that, great as has been our advances in this important affliction of man, there is still need for much further

exploration. If the next decade will be as fruitful as the last, we can surely say that our concepts in management of coronary disease will advance tremendously. The ultimate solution, however, which should resolve this problem is one of basic research seeking to answer the query—what is the cause of atherosclerosis? Furthermore, we need some knowledge regarding the manner in which atherosclerosis can be retarded, and it is not too much to believe that ultimately, perhaps in our lifetime, we will know how to prevent atherosclerosis and thus finally to allow people to die merely of real old age.

# ALLERGY: TRENDS AND THEIR IMPLICATIONS \*

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THE procedures in the present day management of some of the allergic manifestations are chiefly the result of concepts and experimental findings established many years earlier. The chief events responsible for the development of the practice of allergy have been: the demonstration of anaphylactic phenomena at the turn of this century by Hericourt and Richet,<sup>1</sup> Arthus<sup>2</sup> and others; the concept of bacterial allergy advanced by Von Pirquet<sup>3</sup>; the production of the refractory state, or desensitization, in sensitized animals; the attention called by such men as Wolff-Eisner<sup>4</sup> and Meltzer<sup>5</sup> to the resemblance of hay fever and asthma to the anaphylactic symptoms in the guinea pig; and the demonstration of diagnostic possibilities of the whealing skin reaction by Blackley,<sup>6</sup> Schloss,<sup>7</sup> and others. Later, the demonstration of the specific antibody in allergy, the atopic reagin,<sup>8</sup> gave us the explanation of a part of the mechanism of the allergic reaction. Still later, the finding of another antibody, the blocking antibody,<sup>9</sup> which prevented the union of antigen and reagin, gave us the first immunological evidence in support of the mechanism of desensitization in man. These facts, applied first to the etiology, diagnosis and specific treatment of asthma and hay fever, were extended to other conditions such as eczema, contact dermatitis, migraine, urticaria, gastrointestinal manifestations, ophthalmologic diseases and other conditions.

In more recent years certain trends have been emerging in the field of allergy with respect to its practice, its attitudes, its thinking and its concepts. These trends will undoubtedly play a prominent part in the molding of the science and the practice of allergy of the future. It is with that thought in mind that I wish to consider with you some of these trends.

## TREND OF INCREASING PRACTICAL INTEREST IN ALLERGY

In recent years there has been a substantial increase in interest in allergy on the part of the medical profession and the public. Many practitioners who knew nothing and cared less about allergy five or 10 years ago are now attempting to apply allergic management to some of their patients. More and more physicians are groping for some basic and practical knowledge which they can apply to the care of at least some of the simpler allergic problems. The popularity of the short intensive courses in allergy given in the last two or three years under the auspices of the national specialty so-

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the theory that acute articular rheumatism was an allergic manifestation. Weintraub then claimed that rheumatic fever constituted an anaphylactic phenomenon resulting from a reaction to bacterial proteins. Swift and his associates<sup>15</sup> have done extensive experiments which indicate that some of the manifestations of rheumatic fever are due to an allergy to the non-hemolytic streptococcus. The tissue alterations in hypersensitive rabbits and the pathological changes in rheumatic fever are now regarded by many pathologists as strikingly similar. Recently, Rich and Gregory<sup>16</sup> showed that the cardiac lesions produced in rabbits as a result of serum sickness resembled the typical Aschoff bodies of rheumatic fever. Space does not permit the discussion of a number of other infectious diseases in which the allergic concept is receiving attention.

In recent years a number of other pathologic states have been seriously discussed as allergic phenomena. We shall mention only one or two of these. In 1925 Gruber<sup>17</sup> suggested that periarteritis nodosa might be an allergic disease. His claim was based in large part on the presence of eosinophilic infiltrations. Later the allergic concept was strengthened by the reports of the association of asthma with periarteritis nodosa and the finding of high percentages of blood eosinophilia in these patients. Rich and Gregory<sup>18</sup> reported lesions of periarteritis nodosa in patients who died after having had serum sickness or allergic reactions to sulfonamides. When these investigators succeeded in producing similar lesions in rabbits after serum sickness<sup>19</sup> the evidence for the allergic nature of periarteritis nodosa seemed to be fairly complete.

Acute disseminated lupus erythematosus, long regarded as a disease of unknown etiology, is now linked with the concept of allergy by a number of pathologists and other investigators. Fibrinoid degeneration of connective tissue is found by Klemperer and his associates<sup>20</sup> and others to be the outstanding pathologic change in this disease. This degeneration of the collagen is considered by some as a common factor linking this disease with scleroderma and dermatomyositis. Fox<sup>21</sup> reported a case of lupus erythematosus in a girl after serum administration. Teilum<sup>22</sup> presents evidence from the University Institute of Pathological Anatomy at Copenhagen that lupus erythematosus disseminatus is an allergic state, probably due to hypersensitiveness to various bacteria and their allergenic substances. He describes the miliary epithelioid cell granuloma in the serosa as the typical lesion and the primary fibrinoid degeneration of the collagen as the factor common to this disease and rheumatic fever. In dermatomyositis the itching and edema can be presumably explained on the basis of histamine release, although there has been no proof of that. It was interesting to note, however, that we obtained decided relief of the itching in a case of dermatomyositis with the use of one of the antihistaminic agents, pyribenzamine.

## TREND TOWARD CHANGING IMMUNOLOGIC CONCEPTS

The early concept confining the antigen to proteins, especially of large molecular size, is undergoing considerable evolution which is bound to have theoretical as well as practical implications in allergy. Many years ago Landsteiner<sup>23</sup> and his followers demonstrated that a nonprotein substance of small molecular weight could be endowed with specific antigenic properties if it were attached to a larger molecule, usually a protein. This was the hapten concept which gave rise to the current explanations offered for many of the types of drug allergy. In passing, it must be emphasized that as yet there is no conclusive proof that this hapten conjugation *in vivo* is the *modus operandi* in drug allergy. The researches of Heidelberger, and Avery and others then demonstrated without a doubt that complex carbohydrates could also constitute antigens, having many of the properties of protein antigens. Some evidence has also been advanced which indicates that even lipoids can be antigenic.

Then there began to emerge reports here and there indicating that chemical substances of low molecular weight can have antigenic properties. In some instances animals were sensitized with such substances, while in others the manifestations of hypersensitivity were produced by the reapplication of such a chemical. In a series of patients having occupational exposure to a chemical substance of low molecular weight (chloramine) we were able to show not only that it was capable of producing asthmatic symptoms but also that it was able to give specific whealing skin reactions and displayed circulating antibodies.<sup>24</sup> Unless it can be shown that there is a conjugation of this substance in the body, the implication is evident that small molecules can constitute complete antigens and can produce allergy.

And if this latter possibility is correct we shall have to modify our entire attitude toward the search for causes of allergic manifestations. Our current procedures are definitely those aimed at disclosing protein allergy and skin reacting antigens practically exclusively. It is not beyond the stretch of the imagination that we might have to reroute our efforts and technics to include investigations seeking to suspect as allergens the various and relatively simple chemical substances, which may or may not be skin reacting, in foods, coal smoke and other contaminants released in the atmosphere, particularly from industrial plants. As a matter of fact, many clinical observations in allergic patients, such as the bronchospastic effects of coal smoke, some of the benefits of climatic change, and the presence of many cases of allergy with unidentified causes, strengthen the suspicion that atmospheric contaminants may be an important class of allergens.

There are other immunologic studies in progress that may ultimately have a profound influence on the practice and success of allergy. Among these may be mentioned advancement in our knowledge of the nature of antibodies and antigens, and attempts aiming at the improvement and perfection of methods of immunization.

## TREND TOWARD INCREASING MAN-MADE ALLERGY

Beginning primarily with the use of animal serums in medicine, the problem of allergy to therapeutic substances has been rapidly increasing. The countless allergic reactions from the arsphenamines, the allergic reactions from insulin and liver extracts, injectable hormones and vitamins, and the numerous allergic manifestations from the sulfonamides, barbiturates and antibiotics, constitute an incomplete list of our multiplying allergic hazards with each new therapeutic advance.

The range of therapeutic substances is so broad that no practitioner of medicine, whatever his specialty, is now immune from contact with allergic experience. It is in large part these man-made allergic problems which have forced all medical men to the necessity of becoming conversant with some of the phenomena of allergy. We are presented with a problem which is going to increase in importance with the further rapid development of new therapeutic products. It is difficult to say what the final outcome of this situation will be and how we shall learn to combat it. In the meanwhile, a practical and sane attitude should be to discourage the use of sulfonamides, penicillin and other sensitizing agents in trivial ailments, so that the patient will less likely be allergic to that drug when he is in desperate need of it.

Scientific and practical progress in the field of drug allergy might be made more readily because it lends itself to close study, since we are dealing with a group of allergic manifestations in which the etiologic agent is identified and its chemistry known. The phenomena of drug allergy open greater opportunities for observations on the immunologic mechanisms and processes of allergy in general.

## TREND TOWARD A SINGLE THERAPY FOR ALL ALLERGY

The concept of a nonspecific method for the production of specific immunologic response is not new. Hundreds of forms of nonspecific therapy have been advocated from time to time, and some are still in use. For the most part they have been complete failures or impractical of application. In the last decade or so various efforts have been directed at combating the histamine effects of the allergic reaction. The hope that histaminase could be an effective agent has now been dimmed.<sup>25</sup> Although in proper proportions in vitro when in contact for a number of hours histaminase will destroy histamine, the conditions in the living animal are entirely different and such therapy has been judged as useless. Histamine itself does not produce a tolerance to histamine,<sup>26</sup> and critical observers<sup>27</sup> now agree that histamine-azo-protein, meant to increase the tolerance to histamine, also fails in its objective.

At present we are in an era of active interest in anti-histaminic agents. For a number of years investigative work has been going on with the idea of synthesizing compounds which would have competitive action with his-

tamine for cell receptors. As a result of these researches some drugs have been found sufficiently useful to be made available to the general medical profession. Such drugs used clinically in this country are benadryl and pyribenzamine,<sup>12</sup> while in Europe neoantergan<sup>28</sup> and antistine<sup>29</sup> are the representatives in this field.

These drugs are similar in their action, although there are some differences in their quantitative effect and in the intensity of their toxic symptoms. In general, they are effective in the symptomatic relief of a large percentage of patients with urticaria, angioneurotic edema and seasonal hay fever, and are helpful in a lesser percentage of cases of chronic vasomotor rhinitis. They are also useful in eczema and in other forms of itching, such as pruritus ani or vulvae. Their effectiveness in asthma is very slight and rarely reaches the degree of action obtained from epinephrine, ephedrine or aminophyllin.

The fanfare and publicity which accompany the launching of new drugs in our modern times are almost certain to result in the misuse of such drugs. It takes a long while before all medical men and the public learn from experience that initial enthusiasm must be deflated and the limitations of the drug defined. The antihistaminic drugs are still in the phase of enthusiasm. Many allergic conditions for which they are put to use are known to respond very little, if at all to them. Many other conditions for which there is no allergic concept are also being subjected to these drugs, for no other reason than that a new therapeutic agent is available.

All of these histamine antagonists, and other new ones with which we have been experimenting, produce undesirable side reactions, in greater or lesser degree. The most common side reaction is sedation or sleepiness. This is most marked in the case of benadryl and varies with the other drugs. Other side reactions have been dizziness, palpitation, nausea, nervousness, lassitude and insomnia. In many instances these side actions are of sufficient order to make it inadvisable for the patient to continue the use of the drug. More severe toxic effects, such as convulsions, have been also noted. The possibility of remote toxic effects from these drugs is still not a settled question, although there appears to be no decided tendency to it.

These drugs are of some aid in the treatment of allergic manifestations, but it should be noted that they possess objectionable features also. Attempts are being made to produce still newer drugs which will be less toxic, and we are now experimenting with some of these. It must be emphasized, however, that the most perfect of such drugs would only be palliative and should not be confused with the more lasting relief possible by specific desensitization.

The search for an ideal antihistaminic substance has constituted the most decided trend in recent years in the investigation of antiallergic therapy. However, some of our experimental findings in the investigation of antihistaminic agents indicate that there is no direct quantitative relationship



between antihistaminic, antianaphylactic and antiallergic potency. These and other considerations furnish the basis for the belief that other mechanisms in addition to histamine release may be important components of the anaphylactic and allergic reaction. It is necessary, therefore, in the future in the search for antiallergic drugs to use other screening methods in addition to antihistamine activity.

### OTHER TRENDS IN SCIENTIFIC PROGRESS IN ALLERGY

There has always been the necessity and now there is a growing inclination for the allergist to observe and examine the developments in other fields of science so that he may apply them to his own investigations. One of the most fertile fields, of course, is immunology. We have already discussed a few of the immunological phases of interest to allergy. At this point mention should be made of another general trend in allergy and immunology. This may be called the trend for unification. Facts are emerging which tend to decrease the breach between allergic manifestations which had been regarded in the past as totally unrelated. For example, one of the prime differences between atopic allergy, such as in asthma, and bacterial allergy, such as in tuberculosis, had been the failure to find transferable antibodies in the latter. And now with the demonstration that the leukocytes can transfer bacterial allergy the two types of allergic manifestations are brought closer.

In the past the anaphylactic antibody had been sharply delineated from the human allergic antibody. New experimental facts are approximating these antibodies. There is an increasing trend to regard different types of antigens producing different allergic manifestations as behaving in a similar manner. It has also been shown that a number of specific antibodies can be present in the same protein molecule.

Many of the achievements in other scientific fields may contain the clue to the solution of some of our allergic problems. From the facts of physics we are learning how to modify antigens for slower absorption. The development of our knowledge of isotopes should enable us to learn about the fate of antigens and antibodies, the behavior of histamine and many other facts of importance in allergy. The new work of Tiselius on the separation and identification of proteins, peptides, amino acids and other substances by physical adsorption should open the way for many investigations dealing with immunology and allergy.

### SUMMARY

Allergy is attracting increasing interest from the public and medical profession. Because of that we must give greater attention to a consideration of the elementary facts concerning it so that the tendency to misdirection will be minimized. The growing problem of allergy to drugs and injectable substances is forcing almost every practitioner to become conversant with the

field. There is a decided trend to the realization that the concept of allergy is important in the interpretation of the phenomena of many of the infectious diseases. Progress in the synthesis of antihistaminic drugs probably represents only one phase of the trend to attack basic problems in allergy.

There is a growing tendency for those interested in allergy to apply immunologic, pathologic, physiologic, physical and chemical discoveries and methods to advance this science. The field of allergy needs, and holds great promise for, competent clinicians and particularly those who have an imaginative and pioneering spirit. For such men and women many of us will make great effort to provide the requisite stimulation, training and experience.

### BIBLIOGRAPHY

1. HERICOURT, J., and RICHET, C.: Effects lointains des injections de serum d'anguille, *Compt. rend. Soc. de biol.*, 1898, x, 137.
2. ARTHUS, M.: Repeated injections of horse serum into the rabbit, *Compt. rend. Soc. de biol.*, 1903, lv, 817.
3. VON PIRQUET, C.: Allergie, *München. med. Wchnschr.*, 1906, liii, 1457.
4. WOLFF-EISNER, A.: Das Heufieber, sein Wesen und seine Behandlung, 1906, J. F. Lehman, Munich.
5. MELTZER, S. J.: Bronchial asthma as a phenomenon of anaphylaxis, *Jr. Am. Med. Assoc.*, 1910, lv, 1021.
6. BLACKLEY, C. H.: Experimental researches on the cause and treatment of catarrhus aestivus (hay-fever or hay-asthma) 1873, Ballière, Tindall & Cox, London.
7. SCHLOSS, O. M.: A case of allergy to common foods, *Am. Jr. Dis. Child.*, 1912, iii, 341.
8. PRAUSNITZ, C., and KÜSTNER, H.: Studien über die Ueberempfindlichkeit, *Zentralbl. f. Bakt.*, 1921, lxxxvi, 160.
9. COOKE, R. A., BARNARD, J. H., HEBALD, S., and STULL, A.: A mechanism of protection produced in hay fever patients by the injection of pollen extract, *Jr. Allergy*, 1935, vi, 593.
10. SWINEFORD, O., JR.: Undergraduate education in allergy, *Assoc. Am. Med. Coll.*, 1946, xxi, 265.
11. FEINBERG, S. M., and FRIEDLAENDER, S.: Nasal congestion from frequent use of privityne hydrochloride, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1095.
12. FEINBERG, S. M.: Report to the Council on Pharmacy and Chemistry. Histamine and antihistaminic agents, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 702.
13. SPAIN, W. C. in *Cooke's Allergy in theory and practice*, 1947, W. B. Saunders Co., Philadelphia.
14. FEINBERG, S. M.: *Allergy in practice*, 2nd ed., 1946, The Year Book Publishers, Chicago.
15. SWIFT, H. F., DERICK, C. L., and HITCHCOCK, C. H.: Bacterial allergy (hyperergy) to nonhemolytic streptococci in its relation to rheumatic fever, *Jr. Am. Med. Assoc.*, 1928, xc, 906.
16. RICH, A. R., and GREGORY, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity, *Bull. Johns Hopkins Hosp.*, 1943, lxxiii, 239.
17. GRUBER, G. B.: Periarthritis nodosa with especial regard to affection of gallbladder and kidneys, *Virchow's Arch. f. path. Anat.*, 1925, cclviii, 441.
18. RICH, A. R.: The rôle of hypersensitivity in periarthritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 123.

19. RICH, A. R., and GREGORY, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, *Bull. Johns Hopkins Hosp.*, 1943, lxxii, 65.
20. KLEMPERER, P., POLLACK, A. D., and BAEHR, G.: Diffuse collagen disease: Acute disseminated lupus erythematosus and diffuse scleroderma, *Jr. Am. Med. Assoc.*, 1942, cxxix, 331.
21. FOX, R. A.: Disseminated lupus erythematosus—an allergic disease? *Arch. Path.*, 1943, xvi, 311.
22. TEILUM, G.: Pathogenic studies on lupus erythematosus disseminatus and related diseases, *Acta med. Scandinav.*, 1946, cxxiii, 126.
23. LANDSTEINER, K.: Experiments on anaphylaxis to azo-proteins, *Jr. Exper. Med.*, 1924, xxxix, 631.
24. FEINBERG, S. M., and WATROUS, R. M.: Atopy to simple chemical compounds—sulfonechloramides, *Jr. Allergy*, 1945, xvi, 209.
25. Preliminary Report on Histaminase (Torantil), Report of the Council on Pharmacy and Chemistry, *Jr. Am. Med. Assoc.*, 1940, cxv, 1019.
26. WELLS, J. A., GRAY, J. S., and DRAGSTEDT, C. A.: An investigation of the question of histamine tolerance, *Jr. Allergy*, 1941, xiii, 77.
27. COFFIN, G. S., and KABAT, E. A.: The effects of immunization with histamine azoprotein on histamine-intoxication and passive anaphylaxis in the guinea pig, *Jr. Immunol.*, 1946, lii, 201.
28. BOVET, D., HORCLOIS, R., and WALTHERT, F.: Propriétés antihistaminiques de la N-p-methoxybenzyl-N-dimethylaminoethyl a aminopyridine, *Compt. rend. Soc. de biol.*, 1944, cxxxviii, 99.
29. MEIER, R., and BUCHER, K.: Pharmakologie des 2-(N-phenyl-N-benzylaminoethyl)-imidazolins (Antistin). (Ein neuer synthetischer Antihistaminkörper), *Schweiz. med. Wchnschr.*, 1946, lxxvi, 294.

# SPLENOMEGALY IN CONGESTIVE HEART FAILURE \*

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DURING the past few years, we have noted several instances of palpable spleen in patients with chronic cardiac decompensation; no other reason for splenic enlargement was found in these cases.

It has long been a general impression that the spleen does not become palpably enlarged as a result of congestive heart failure alone. As a corollary of this, it has been felt further that if the spleen is palpable in a case of heart failure, some complication should be suspected. This statement was made by Held<sup>1</sup> in his discussion on splenomegaly, and the same opinion was voiced by Rolleston.<sup>2</sup> Talley and Lindsey<sup>3</sup> studied 198 adults with congestive heart failure, and found palpable spleens in only three. Comroe<sup>4</sup> did not list congestive failure as a cause of splenomegaly in adults. Fishberg<sup>5</sup> stated that it is doubtful that the spleen ever becomes palpable in congestive failure alone, but admitted that changes in the liver secondary to cardiac decompensation may produce a spleen that is sufficiently enlarged to be felt. He also said that the spleen is often small and atrophic in long-standing congestive failure. Similar statements were made by Boyd<sup>6</sup> and MacCallum.<sup>7</sup> Klemperer<sup>8</sup> indicated that the spleen is occasionally enlarged in congestive failure of great duration, but that it is often smaller than normal. Ravenna<sup>9</sup> made a similar comment.

However, not all writers have agreed with these views. Barker<sup>10</sup> has reported a case of rheumatic heart disease in chronic decompensation with a palpable spleen. There were no apparent complications in his case. Barron and Litman<sup>11</sup> found spleens weighing over 300 grams in 10.4 per cent of 1505 autopsied cases of chronic cardiac disease. Arnett<sup>12</sup> found the spleen enlarged in 23 per cent of cases of chronic non-infectious heart disease.

With the above points in mind, a review was made of the records of the Department of Pathology at the Peter Bent Brigham Hospital. All cases were selected from admissions to the medical and surgical wards of the Peter Bent Brigham Hospital who subsequently came to autopsy. The cases selected were divided into four groups. The first group is composed of 50 patients from the surgical service. These were used to determine the normal average weight of the spleen. Cases of congestive heart failure, myocardial infarction, or in whom congestion of the viscera was diagnosed pathologically are excluded from this group. The second group comprises 50 cases of valvular rheumatic heart disease; only cases with both clinical and pathological evidence of congestive heart failure were included in this group. The

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third group is composed of 50 cases of hypertensive or arteriosclerotic heart disease diagnosed pathologically or clinically and confirmed at necropsy. The fourth group comprises 46 cases of subacute bacterial endocarditis. These were included in order to determine the relative size of the spleen in this disease, in which the frequent occurrence of a palpable spleen is widely recognized. Patients under 16 years of age were not included. Cases in which there was found either clinical or pathological evidence of diseases often associated with splenomegaly were excluded. Subacute bacterial endocarditis was excluded from the first three groups. Also excluded were cases not admitted to the wards, cases in which the spleen was not weighed, and five cases in which the necessary pathological data were not available. Patients with congestive failure of less than one month's duration, and those having a recent myocardial infarction as the only cause of decompensation were omitted.

TABLE I

	Group 1. 50 Surg. Cases Normal?	Group 2. 50 Rheum. Heart Disease	47 Rheum. Heart Disease	Group 3. 50 Non- Valvular Heart Disease	Group 4. 46 Sub. Bact. Endocarditis
Average weight of spleen in grams	135	220	210	198	371
Number spleens over 200 grams	9	23	20	19	39
Number of spleens over 300 grams	None	9	7	6	30
Number spleens infarcted	—	8	8	6	22
Average weight infarcted spleens in grams	—	239	239	197	—
Average weight of spleen in cases with failure 3 years or over	—	—	228 (31 cases)	190 (14 cases)	—
Average weight pt. in kg.	68 (36 cases)	—	67 (34 cases)	71 (32 cases)	68 (40 cases)
Average age pt. in years	56	47	—	56	—
Number livers over 1600 grams	—	19	16	20	—
Number livers over 1900 grams	—	9	7	11	—
Average weight liver in grams	—	1487	1460	1608 (49 cases)	—

In all cases of congestive failure, the weight and histology of both spleen and liver were noted. When available, the ages and weights of patients in all groups were recorded, since both these factors influence spleen size.<sup>13</sup> Weights were taken from a period of relative good health. The duration of the symptoms of congestive failure was also recorded, in order to determine whether this is a factor influencing the size of the spleen.

*Findings.* Results are summarized in table 1. The average spleen size in the surgical control group was found to be 135 grams. In the 50 cases of rheumatic valvular heart disease, the average spleen weight was 220

grams. Excluding the three cases of microscopic biliary cirrhosis found in this group, the average spleen weight fell to 210 grams. In the hypertensive and arteriosclerotic heart disease group, the average weight was 198 grams. In subacute bacterial endocarditis, the average was 371 grams.

Barron and Litman,<sup>11</sup> in their study on hepatomegaly and splenomegaly, considered any spleen over 200 grams to be enlarged, and any of 300 grams weight or more, to be in the range of clinical palpability. Fifteen per cent of the spleens in the entire congestive failure group were in the range of theoretical palpability; upon exclusion of the three cases of biliary cirrhosis, this figure falls to 13.4 per cent. It is of interest to note that only one of these 15 spleens was actually felt on the ward, although one weighed 700 grams, another 625 grams, and another 500. This is probably explicable on the basis that these patients were examined within a few days or weeks of death and were unable to cooperate; in addition to this, most were orthopneic, and many had ascites and edema of the abdominal wall. Still another factor hindering the palpation of the spleen in a patient with cardiac decompensation is his impaired vital capacity and inability to move his diaphragm fully. The ages and weights of the patients in the first three groups were felt to be sufficiently similar to permit of their elimination as a factor in determining the size of the spleen. Duration and type (i.e. valvular or non-valvular heart disease) seemed to play no great part in determining the weight of the spleen at autopsy. Among the cases of rheumatic heart disease, there were eight showing splenic infarctions; in these the average spleen weight was 239 grams. Splenic infarctions were found in six of the non-valvular heart disease group; here, the average spleen weight was 197 grams. In neither instance did the presence of infarctions seem to play a great part in influencing the weight of the spleen.

In the rheumatic valvular group, cardiac cirrhosis was found in 11 instances; in these, the average spleen weight was 300 grams, considerably above the group average. All these patients had histories of congestive failure for at least six months prior to death, and the average duration of their failure was 4.6 years. If the cases of biliary cirrhosis, two of whom also had cardiac cirrhosis, are removed from this group, then the average weight of the spleen falls to 274 grams. Only one case of cardiac cirrhosis was found in the non-valvular heart disease group; here the spleen weighed 420 grams.

Barron and Litman<sup>11</sup> found spleens weighing over 300 grams in 85 per cent of 87 cases of subacute bacterial endocarditis. Blumer<sup>14</sup> determined that 74 per cent of 220 cases of subacute bacterial endocarditis showed splenic enlargement by either palpation or percussion. Arnett<sup>12</sup> found at autopsy that 51 per cent of the spleens in his series were enlarged in this disease. He used as his criterion of splenic enlargement an increase of 50 per cent above the average size. In this group of 46 cases of subacute bacterial endocarditis, spleens weighing over 300 grams were found in 65.2 per cent of the cases.

Gray<sup>15</sup> considers 1600 grams to be the upper limit of weight for the normal liver; Barron and Litman<sup>11</sup> give 1900 grams as their upper normal for this organ. By their standards, Barron and Litman<sup>11</sup> found hepatic enlargement in only 8.5 per cent of their 1505 cases of heart disease, but found splenic enlargement in 10.4 per cent of these cases. Arnett<sup>12</sup> found 23 per cent of the spleens enlarged in chronic cardiac disease, but livers enlarged in only 17 per cent, using an increase of 30 per cent above the average as his criterion of hepatic enlargement. Smith and Levine<sup>18</sup> found the average weight of the liver in 32 cases of tricuspid stenosis to be only 1535 grams. The number of livers exceeding 1600 grams and exceeding 1900 grams in the cases of congestive failure in this series is given in table 1. It is of interest to note that the weight of the average liver in the hundred cases of congestive failure is not above normal. The fact that the liver is frequently felt clinically in congestive heart failure, and yet is not on the average enlarged by weight at necropsy is difficult to explain. Ptosis of the liver may be one factor involved in this apparent paradox. Probably a more important factor is the loss of blood from the liver before it is weighed in the course of a postmortem examination.

#### SUMMARY AND CONCLUSIONS

1. The spleen, on the average, is increased above the normal size in uncomplicated heart failure.

2. The splenomegaly of cardiac decompensation is apparently not greatly influenced by either the duration of the congestive failure nor by the presence of infarctions in the spleen.

3. In 13.4 per cent of 97 cases of uncomplicated congestive failure, the spleen was found to be large enough to be theoretically palpable, i.e., over 300 grams.

4. The spleen, on the average, shows greater enlargement than does the average liver in cardiac decompensation.

5. Other than actual congestion of the spleen and the presence of cardiac cirrhosis in the liver, no satisfactory explanation for the occurrence of splenomegaly in congestive heart failure is found.

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#### BIBLIOGRAPHY

1. HELD, I. W.: A discussion on the splenomegalies, *Med. Clin. North Am.*, 1919, iii, 519-549.
2. ROLLESTON, H. D.: Discussion on splenic enlargements other than leukemia, *Brit. Med. J.*, 1908, ii, 1157.
3. TALLEY, J. E., and LINDSEY, W. H.: Splenic enlargement in chronic cardiac disease, *Jr. Am. Med. Assoc.*, 1924, lxxxiii, 423-425.
4. COMROE, B. I.: Diagnosis of diseases associated with enlargement of the liver or spleen, *Med. Clin. North Am.*, 1936, xx, 295-305.

5. FISHBERG, A. M.: Heart failure, 2nd Edition, 1940, Lea and Febiger, Philadelphia.
6. BOYD, W. A.: The pathology of internal diseases, 4th Edition, 1944, Lea and Febiger, Philadelphia.
7. MACCALLUM, W. G.: A textbook of pathology, 7th Edition, 1940, W. B. Saunders, Philadelphia.
8. KLEMPERER, P.: The spleen, in DOWNEY, H.: Handbook of hematology, 1938, Paul B. Hoeber, Inc., New York.
9. RAVENNA, P.: Splenoportal venous obstruction without splenomegaly, Arch. Int. Med., 1943, lxxii, 786-794.
10. BARKER, L. F.: Chronic valvular disease of the heart (double mitral and double tricuspid lesions) of rheumatic origin, with signs of cardiac failure and with palpable spleen, Med. Clin. North Am., 1930, xiv, 215-217.
11. BARRON, M., and LITMAN, A. B.: Importance of hepatomegaly and splenomegaly in differential diagnosis, Arch. Int. Med., 1932, l, 240-256.
12. ARNETT, J. H.: Splenic and hepatic enlargement in endocarditis: a study of 286 autopsy findings, Am. Jr. Med. Sci., 1922, clxiii, 590.
13. ELMER and ROSE: Physical diagnosis, 7th Edition, 1935, C. V. Mosby, St. Louis.
14. BLUMER, G.: Subacute bacterial endocarditis, Medicine, 1923, ii, 105.
15. GRAY: Anatomy of the human body, 24th Edition, 1942, Lea and Febiger, Philadelphia.
16. SMITH, J. A., and LEVINE, S. A.: The clinical features of tricuspid stenosis, Am. Heart Jr., 1942, xxiii, 739-759.



# PROBABLE GENETIC PREDISPOSITION TO VIRAL PNEUMONIA \*

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OBSERVATIONS from time to time suggest unusual susceptibility among members of families to certain infectious diseases. Although it is often difficult to separate hereditary influences from environmental ones, the high incidence of tuberculosis, leprosy, colds,<sup>1</sup> pneumonia,<sup>2</sup> poliomyelitis and especially of rheumatic fever among persons of certain genetic groups seems to depend upon a combination of inherited susceptibility, environment and exposure to common sources or to each other. The following observation of a close succession of attacks of viral pneumonia among females in direct line of descendance seems to portray such an occurrence.

The family group consisted of the grandparents, three daughters and their husbands, and four grandchildren as illustrated in the figure. The grandmother became sick in Florida about January 1, 1946, with chills, fever, headache, sore throat, blocked nose and persistent cough. She returned to her home in Philadelphia January 5, 1946, and was admitted to the hospital January 11, 1946. Between January 5 and 11 her daughters and their husbands were exposed to infection during repeated visits at her bedside, and could obviously have served as indirect carriers of infection to the children in their own homes. The first of the apparent indirect contact infections occurred in granddaughter, S. F., on February 1, between two and three weeks later, which is the supposed incubation period of certain forms of viral pneumonia.<sup>1</sup> In the subsequent 10 days, four other apparent direct or indirect contact infections began. The dates of onset of disease in the six patients and the probable nature of contact were as follows:

Grandmother, M. B., Aged 52, January 1	
Granddaughter, S. F., Aged 9, February 1.....	Indirect Contact
Daughter, B. F., Aged 34, February 2.....	Direct Contact
Daughter, M. R., Aged 29, February 3.....	Direct Contact
Daughter, R. S., Aged 31, February 5.....	Direct Contact
Granddaughter, E. R., Aged 9 mo., February 10.....	Indirect Contact

The disease was of the severe form in each of the six female patients and no evidence of infection either mild or severe occurred in the six corresponding male members of the exposed family group as shown in the figure, nor did it occur in the immediate community before, during or after the episode. The attacks in all six patients were characterized by the usual features of viral pneumonia with rather sudden onset; dry, persistent, or paroxysmal

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nonproductive cough; dyspnea, cyanosis, high fever, photophobia, sweating, normal number of leukocytes, and roentgen evidence of bilateral pneumonia.<sup>1</sup> One patient, B. F., was alarmingly sick with fever of 40° C. (104° F.) and periods of peripheral vasomotor collapse. The disease lasted from 15 days in E. R., to 39 days in M. B. All recovered uneventfully.

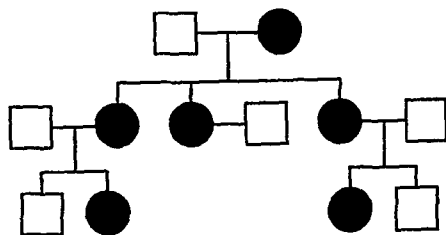


FIG. 1. Members of three generations of a family group. The black discs represent sick females; the squares, the unaffected males.

### COMMENT

Although it is impossible to prove the existence of specific genetic susceptibility to viral pneumonia in the patients mentioned, the sequence of attacks in each of the female members in direct line of descendance and the escape of the equally exposed male members whether genetically related or not, strongly suggests its operation. The occurrence represents a localized outbreak of a form of viral pneumonia contracted at a distant place and carried by a patient into a family group. The individual attacks were all severe and no instances of mild, non-pneumonic forms were detected, nor did the disease spread outside the family group. The circumstances further illustrate the contagiousness of the severe sporadic form of viral pneumonia for susceptible persons of various ages and its relatively long incubation period, assuming that M. B. was the direct source of infection for the daughters and the indirect source for the granddaughters.

### SUMMARY

Attacks of severe viral pneumonia occurred in close succession in six genetically related female members of a family. Corresponding male members escaped infection. The occurrence suggests that a genetic predisposition to the disease existed in these patients.

### BIBLIOGRAPHY

1. SARGENT, F., LOMBARD, O. M., and SARGENT, V. W.: Further studies on the stability of resistance to the common cold: the importance of constitution, *Am. Jr. Hyg.*, 1947, xlv, 29-32.
2. BECKER, E. G.: Pneumonien bei Twillingen, *Ztschr. f. Konst.-Lehre*, 1938, xxxviii, 77-95.
3. REIMANN, H. A.: Primary atypical pneumonias of viral origin or of unknown cause. Viral (virus) pneumonias, nonbacterial pneumonias, in *Internal Medicine*, by J. H. Musser, Ed. 4, 1945, 118-125.

# THE MANAGEMENT OF HYPERTENSION \*

By PAUL D. WHITE, F.A.C.P., *Boston, Massachusetts*

IN 1892, fifty-five years ago, William Osler,<sup>1</sup> in the first edition of his noted textbook on *The Principles and Practice of Medicine*, had the following advice to give concerning Bright's disease, with particular reference to cases with "persistent high tension."

*Treatment.* Patients without local indications or in whom the condition has been accidentally discovered should so regulate their lives as to throw the least possible strain upon heart, arteries, and kidneys. A quiet life without mental worry, with gentle but not excessive exercise, and residence in an equable climate, should be recommended. In addition they should be told to keep the bowels regular, the skin active by a daily tepid bath with friction, and the urinary secretion free by drinking daily a definite amount of either distilled water or some pleasant mineral water. Alcohol should be strictly prohibited. Tea and coffee are allowable.

"The diet should be light and nourishing, and the patient should be warned not to eat excessively, and not to take meat more than once a day. Care in food and drink is probably the most important element in the treatment of these early cases.

"A patient in good circumstances may be urged to go away during the winter months, or, if necessary, to move altogether to a warm equable climate, like that of southern California. There is no doubt of the value in these cases of removal from the changeable, irregular weather which prevails in the temperate regions from November until April.

"At this period medicines are not required unless for certain special symptoms. Patients derive much benefit from an annual visit to certain mineral springs, such as Poland, Bedford, Saratoga, in this country, and Vichy and others in Europe. Mineral waters have no curative influence upon chronic Bright's disease; they simply help the interstitial circulation and keep the drains flushed. In this early stage, when the patient's condition is good, the tension not high, and the quantity of albumen small, medicines are not indicated, since no remedies are known to have the slightest influence upon the progress of the disease. Sooner or later symptoms arise which demand treatment. Of these the following are the most important:—.....

.....  
In cases with persistent high tension the diet should be light, an occasional saline purge should be given, and sweating promoted by means of hot air or the hot bath. If these measures do not suffice, nitroglycerin may be tried, beginning with one minim of the one per cent solution three times a day, and gradually increasing the dose if necessary. Patients vary so much in susceptibility to this drug that in each case it must be tested, the limit of dosage being that at which the patient experiences the physiological effect. As much as ten minims of the one per cent solution may be given three times a day. In many cases I have given it in much larger doses for weeks at a time. I have never seen any ill effects from it. If the dose is excessive the patients complain at once of flushing or headache. Its use may be kept up for six or seven weeks, then stopped for a week and resumed. Its value is seen not only in the reduction of the tension, but also in the striking manner in which it relieves the headache, dizziness, and dyspnoea."

\* Read at the Annual Meeting of the American College of Physicians, Chicago, April 30, 1947.

Now, in 1947, we are still a long way from what will be the final advice for the treatment or, better still, for the prevention of high blood pressure. And yet, despite our ignorance and our uncertainties during the evolution of our knowledge of this condition and its treatment, it is well now and then to pause a moment and to survey the current attempts to manage hypertension. Hence with no air of finality but with an effort at unprejudiced presentation I shall make some remarks about the treatment of the kind of hypertension that we call essential, the fundamental cause or causes of which are still obscure. I shall not deal with the known causes of high blood pressure or with its common and serious complications, namely hypertensive heart disease and failure, apoplexy, and renal insufficiency. I shall, however, refer to the degree of severity of the hypertension from the transient benign to the sustained malignant and to the relationship to age and arteriosclerosis.

The most important consideration at the start concerns the education of the patient. There are those who believe that it is wisest to conceal from the patient the fact that there is hypertension or at least to hide its severity and never to tell what the actual pressure readings are, except to relatives, especially since so many of these patients are very nervous to start with. I have tried different methods of procedure and have found it more satisfactory in the long run to keep my patients, who are an intelligent lot of people, informed in most instances about the general status of their pressure but with detailed discussion as to its variability and the relative unimportance of the actual figures on any one occasion. To leave the pressure a mystery is usually more worrisome to people than to take them into our confidence, whereby we can also more readily elicit their coöperation in the treatment, especially now-a-days when we can really do something quite effective on occasion. In days gone by when we could do little but palliate, there was some point in discouraging patients from having their blood pressures measured more than once in a dog's age after the initial high reading. Recently in a rereëxamination of cardiovascular rejectees (for the army) originally turned down for military service early in World War II because of hypertension or other cause we found a number of cases with slight hypertension and advised, besides reduction of obesity, an annual or even semi-annual check-up of the blood pressure in the future to catch a more serious rise and then to institute more specific treatment.

The next consideration is that of the way of life and the regimen to be advised. This will, of course, vary greatly from slight restrictions only, if the pressure is borderline or but little increased, to complete rest for extreme hypertension with threatened failure of heart, brain, or kidneys. In general, it is still found helpful to establish a program of leisure, if such is possible, for routine daily living or at any rate to insist on frequent rests or vacations which may come at weekends, long or short, monthly, or for a week or two at a time every three months. The hours of work and the intensity of work should both be reduced; it may be necessary, for example, to advise

doing two or three hours of work daily in four or six hours, or four hours in eight, instead of what is so common to these individuals, namely crowding 24 hours into 12 or 16 every day.

A pleasant prescription of ancient vintage is to order a three or four weeks' stay at the baths somewhere twice a year. Thus at some delightful spot in the country with well regulated diet, rest, exercise, and baths many thousands of patients with hypertension have, doubtless for centuries, kept their pressure under fair control and may very well have avoided the need of more radical measures now in vogue. Last summer in Czechoslovakia I visited many famous spas, some with special reputation for helping hypertensive patients. Mackenzie<sup>2</sup> used to deride the spas because of their frequent exploitation and thought that about as much help could come by putting the salts in the bathtub at home, but while expressing his annoyance with the exaggerated commercialism of his day he did admit the favorable effect of these bath resorts as vacation centers with pleasant and relaxing music and beautiful scenery for those patients who were not too ill. As a minor but definite factor the hydrotherapy itself must be taken into consideration—the myriad little bubbles of the CO<sub>2</sub> baths can relax the patient and reduce the blood pressure for the time being.

Physiotherapy of other types at these bath resorts or at home can be another weapon favoring relaxation; massage and osteopathy undoubtedly can act thus but probably the best of such measures is mild exercise itself, unhurried and enjoyed, something that distracts the mind like fishing, or bathing, or exploring fields and forests on foot or horseback. A regular program can be fruitfully laid out for the mildly or moderately hypertensive person. If such an individual can be made to see the value of such relaxation early in his or her hypertension it is quite possible that the evolution of the disease can be altered, although it is as yet difficult to speak with certainty because of the lack of well controlled studies along this line. On the other hand, many of the games that nervous hypertensives seem to like to play such as cards are overstimulating and probably wisely omitted. Many of these seemingly minor details of life are very probably important to consider in the overall planning of the hypertensive's life.

For this life planning I would like to digress a moment and advise the institution of preventive medical measures for the young hyperreactors as well as for the obvious hypertensives, for it is from that group that the true hypertensives of the future spring. It is probably not going too far to give similar advice to the children of hypertensive parents, especially if both parents are hypertensive.

I have spoken of exercise and play and relaxation and physiotherapy but not of rest per se. It is, however, obvious that sedation and sleep are important since in our hypertensive work-up studies we often obtain absolutely normal blood pressure readings during deep sleep (from amytal) in severely hypertensive patients. There is a limit of time, of course, to pre-

scribe for bed rest each night and even in the day, but it should be possible to advise nine or ten hours in bed every night, with rare exceptions, and an hour's rest in the middle of the day before or after luncheon. If sleep evades the patient at times a hypnotic medicine will usually help.

Diet I shall discuss shortly but there are a few habits to be mentioned briefly first. Smoking tobacco usually constricts the peripheral arterioles, cools the skin, and sends the blood pressure up, even as much as 20 millimeters or more. Since that generally happens and since it seems rather silly to maintain a higher pressure throughout the day and evening by smoking a cigarette or even a cigar every hour or oftener, I advise my hypertensive patients to omit tobacco for good; half way measures are usually inadequate, but on occasion I have carried out pressor tests with tobacco in some of my more obstinate habitués and in rare cases there does seem to be very little or no effect.

Coffee and tea can be similarly tested if one wishes, though as a rule they seem to have no harmful effect, and the same is true of alcohol except in excess; as a matter of fact alcoholic drinks may have a favorable or sedative effect, but care should be taken that they do not put weight on these hypertensive patients who so often are inclined to be heavy anyway.

I may have seemed to have spent an undue amount of time this afternoon on the old and recognized measures of therapy such as Osler himself discussed, but I have done so intentionally for two reasons. In the first place, it is quite possible that some hyperreactors may be kept from becoming hypertensives by early heed to these things, and secondly, in the course of the current interest in radical measures of treatment, surgical and dietetic, there can easily be a neglect of these simpler measures, which though perhaps not curative can be helpful in adding their usefulness to the overall treatment, especially when the radical measures may have failed as they sometimes do, or may have been only partially successful.

Now for the rest of the time I shall speak of four measures which are at present creating a good deal of interest in this country but often in rather limited areas geographically or medically. The first of these is psychotherapy. My good friend Carl Binger of New York City has been one of the most active explorers in this field and wrote me only a few days ago that he has little to add to an article published in 1945<sup>3</sup> in the New York Academy of Medicine Bulletin. He states that "the therapeutic results look promising, but it is too early to say." He had been associated with a group who carried on an intensive study<sup>4</sup> of the personality of 24 hypertensive patients, who showed from early life, before hypertension developed, an acute and chronic "failure of the integrative functions of personality which seemed to result from the inefficiency of the patterns of defense against anxiety and the weakness of the repressive mechanisms." One wonders how many persons with similar personalities do not have hypertension and if some hypertensives are exceptions to this pattern.

In 1945 Binger<sup>3</sup> wrote:

"The problem is that of treating a severe character neurosis in which anxiety, depression and suppressed aggression are the cardinal psychopathological features. The method of choice will vary from cheerful neglect (based on that much vaunted common sense which we are all supposed to possess in such good measure) to deep psychological exploration. The latter you will grant is a matter for the expert. What is to be hoped from it we cannot say. There is as yet no evidence that psychoanalysis or any other psychotherapeutic procedure can reverse the physiological process or change the destiny of this disease—be it benign or malignant. The problem is an open one. It needs further investigation. The ground has now been cleared for such an undertaking. It is probable that we can do more by way of prevention than cure.

"There is evidence that a correlation exists between levels of pressure and emotional disturbance and that suitable psychotherapy can ameliorate some symptoms: such as headache, fatigue, palpitation, dizziness, shortness of breath and the fear which these engender." . . .

"Leaving now out of consideration all efforts at deeper psychodynamic inquiry and turning to the every day handling of these patients, I believe that our new knowledge can be put to effective use. We are dealing with tender vessels. They need to be protected from emotional strain, especially from demands upon a self-reliance they do not possess. There is no good in telling them to 'buck up' and 'forget it.' They need the maximum of reassurance about the disease itself. They need very much to feel that some one person is watching over them and will take on his shoulders the burdens of their worries. They need to be encouraged to express their aggression, not by hurling dishes or epithets at their wives, but by directed work and play and by physical exercise, if this is compatible with their cardiac reserve. They need to be weaned away from an over-concern with the level of their blood pressure. The experienced doctor will vary his methods. With some he will be frank, with others he will be silent and to some he will have to dissemble. The manner in which this frightening fact is first presented to them is of the utmost significance. If the doctor shows his own alarm when the mercury column tops 220 it is likely to be communicated at once to his patients.

"It is well to remember that almost all our therapy is in essence psychotherapy. Drugs and sedatives, rest and exercise, diet and baths all have psychotherapeutic implications; and this is just as true of surgery. The surgical amphitheatre has become the court of last resort in this illness. Perhaps in time we will learn on what findings nature bases her verdict—why some patients respond to sympathectomy with a reduction in blood pressure, a recession of retinitis and a merciful relief from headache, while others do not. I hope that it will not be thought too 'tender-minded' of me if I suggest that the attitude which patients bring to the ordeal of operation may in some measure determine its effect upon them. For there are those who face it as they would doom and there are others who look upon it as a deliverance."

Next let us consider in order diets and medicines, both of which have been used in the treatment of hypertension ever since it was first discovered and indeed even before it was discovered *per se*. The first and obvious and as a matter of fact one of the most useful of all the diets has been that of low caloric value for the simple reduction of weight. It has long been known that the reduction of weight and the reduction of blood pressure in obese hypertensive patients often go hand in hand, and as an effective and helpful, though infrequently curative, measure a reduction diet stands high. Next

in point of origin, I believe, comes a low protein diet. It was quite natural to think that if the kidneys were damaged or under strain they should be spared extra effort of getting rid of excessive nitrogenous waste. However, such diets, although common and often spontaneously adopted by the layman who avoided red meat, were not strictly followed as a rule and on two counts were sometimes combated: (1) a man may live on meat and fat and nothing else for years and remain well, free of kidney disease and hypertension, and (2) if albumin is being lost freely in the urine in a case of hypertension extra protein may be helpful in counteracting such loss. Then came the early trial of a low salt diet for hypertension by Allen<sup>6</sup> and his colleagues, generally ignored by the profession at large. And now during the past few years there has been a revival of the interest of the dietary treatment of hypertension, with strict quantitative limitation of salt and protein.

To give you the latest news from several centers where such diets are being studied I shall quote with permission of the senders from telegrams received but a few days ago. Tinsley Harrison<sup>6</sup> with whom Dr. Grollman is associated at Dallas, Texas, wrote as follows: "Drastic sodium restriction of little or no value in severe hypertensives or in older patients. Will lower blood pressure in many young subjects and to normal level in some. Restriction must be so drastic that diet is rather impractical except for experimental use. Apparently the rice diet acts by virtue of low sodium content." Selye<sup>7</sup> wired from Montreal as follows: "Thus far dietary treatment only in animals. Clinical work limited to ammonium chloride therapy. We have found increased sodium to chloride ratios in some hypertensives analogous to hypochloremic alkalosis of Cushing's disease. In all patients with such an increase and in some with normal ratios such treatment has been of benefit. Paper about to be published." He has been treating his younger hypertensive patients for several months according to the following plan:

- "1. a low salt diet (no extra salt in cooking or at table).
2. a low protein diet (only one helping of meat, fish or fowl or 1 egg per day, plus ordinary intake of vegetable protein). Caloric intake is amplified by carbohydrate as indicated.
3. 6 gm. of ammonium chloride per day in doses of 1½ gm. t.i.d. p.c. and at bedtime."

From Cleveland Corcoran and Taylor,<sup>8</sup> working with Page, wrote me as follows: "In our experience no specific effect of rice. Correction of obesity definitely effective. Correction of nitrogen and sodium retentions where renal status indicates very desirable."

Because of the considerable experience during the past four or five years of Dr. Kempner of Duke University at Durham, North Carolina, in the treatment of hypertensive patients with a strict rice diet and because of his reported success in a good many cases I myself made a pilgrimage to his clinic a month ago, saw some of his cases, and had a sample rice meal at one of



the rice houses in town. Kempner<sup>9</sup> introduced this diet some seven or eight years ago in the treatment of patients with renal disease and insufficiency because of both low protein and low sodium content and of the easily assimilated protein in the rice itself. The diet consists of rice, white or brown, boiled carefully for 20 minutes, served hot and relatively dry, 8 ounces or thereabouts a day in three courses with fresh or frozen fruits of nearly all kinds, and sugar more or less ad lib, to bring the total calories to 2,000 or a bit more. Between meals one may munch on rice-brittle candy. No meat, vegetables, milk, or salt is allowed for the first six weeks or so and then the diet may be gradually liberalized with two potatoes and a few ounces of meat weekly. Later if the blood pressure stays down one-third of the fruit is replaced by vegetables and more meat is given. There are only 20 grams of protein and far less than a gram of salt in this initial diet daily, and yet in many patients such limitation after they become accustomed to it and if they are willing to stick it out does not seem to cause any particular hardship, and light or even average work can be resumed without trouble. It is reported that about two-thirds of those hypertensive patients who are willing to give this diet a fair trial are distinctly helped by it subjectively and in blood pressure levels, and in some cases cardiac enlargement and eyeground abnormalities decrease or clear away and the electrocardiogram improves. Thus hypertensive heart disease has been proved to be reversible by the rice diet as well as by lumbodorsal sympathectomy.

I might add that I found the one meal on the diet that I took myself quite palatable and that I believe I would be willing to stick it out for a long time, with liberalization when circumstances permitted, provided it made me feel better and provided my blood pressure were significantly reduced thereby. I saw cases who had achieved a normal blood pressure by this therapy who had failed by other procedures, and it seems fair to me to suggest to some individuals, especially to those who are obviously unsuited for surgery, to try this diet; in fact it is quite reasonable to try this first for if it proves unsuccessful it is still possible to operate. Although the diet is difficult to take, surgery may be even more so. At the same time, of course, the measures that I have outlined at the beginning of the paper may be carried out concurrently and may appreciably help the dietetic effect.

Now let us turn to drug therapy. The obvious medicines and the ones that have been used most for many years are the sedatives and the nitrites. Bromides, but especially the barbitals, have been given and in particular phenobarbital, not only to induce sleep at night but also as rations through the day and with effect. We cannot, of course, maintain sedation heavy enough in most cases to keep the blood pressure of hypertensive patients at a normal level but even the smaller doses that are feasible, e.g.  $\frac{1}{4}$  to  $\frac{1}{2}$  grain of phenobarbital three or four times a day, do help some, and this is a disease that needs attack from various directions in default of a specific cure as yet. The opiates except in crises should be avoided. Papaverine as an antispasmodic has been disappointing.

The nitrites do lower the pressure but as a rule too transiently or mildly in hypertension to make them worth while, and effective doses are likely to give headaches. The slowly acting mannitol hexanitrate has resumed some degree of popularity but we must await further proof of its effectiveness before accepting it for routine use.

The drug that has been periodically most popular during the past 20 years and which does lower the blood pressure somewhat in some cases is thiocyanate of potassium. It is, however, often disappointing and can in the more effective dosage be quite toxic. Also now that blood levels can be measured it should not be given without such occasional check.

Many other medicines for hypertension in the past have come and gone. Some have depended on the enthusiasm of some individual or countryside, some have been traditional, and some have helped certain complications or side-effects of the hypertension. None has been widely and permanently adopted although perhaps some should be subjected to more careful and critical pharmacological testing. Included among these drugs are garlic, pumpkin seed, watermelon seed, sunflower seed, mistletoe, *veratrum viride*, potassium iodide, theobromine and theophylline, benzyl benzoate, renal and other tissue or organ extracts, vitamins, and endocrine preparations, including the sex hormones.

Finally, we come to the newest of the drugs being tried in hypertension today, including tetraethyl ammonium salts and priscol. These chemicals have a physiologically sympathectomizing effect and eventually one may be found that will bring the blood pressure down to normal for a long enough period without important and disturbing by-effects to be introduced for routine periodic use. As yet nothing adequate has been found and the testing must still be regarded as in the experimental stage although many workers are hot on the trail.

Last but not least among the therapeutic procedures for hypertension is the surgical measure of sympathectomy. Other surgery such as renal decortication and unilateral nephrectomy has not relieved essential hypertension itself. Nor has irradiation of the adrenal glands, although spectacular relief has been achieved on occasion by excision of a pheochromocytoma. Introduced by Rowntree and Adson<sup>10</sup> over 20 years ago sympathectomy has slowly evolved from its disappointing early status to its present effective position, largely because of Smithwick's introduction<sup>11</sup> over seven years ago of the more extensive procedure of lumbodorsal sympathectomy which has been worthwhile in two-thirds to three-quarters of the patients operated on by Smithwick, or more so still in the younger cases with high diastolic and low pulse pressures and good renal function. It has been life-saving in a considerable number of my patients who had already developed hypertensive heart disease, and a few years ago established more than had any other experience my realization of the not infrequent reversibility of heart disease. Uncommonly hypertensive patients will spontaneously lose their hypertension in the course of years, but my observation of cases subjected to lumbo-

dorsal sympathectomy or perhaps to the rice diet too has been a new experience in the past few years. It is to be hoped that something easier than either the lumbodorsal sympathectomy (or the rice diet) may be found in the near future to control the devastating effect of hypertension which still remains in this country and in the world at large one of the chief causes of disability and death.

I have finished this brief review of the management of hypertension. It is obvious that we still have a long way to go and a lot to do before we shall have achieved our goal. Meanwhile we should avail ourselves of all the measures that have been proved worth while from the simple but important planning of the way of life in early cases or in preventive medicine to the more radical and lifesaving measures in serious cases whose days are otherwise numbered.

#### BIBLIOGRAPHY

1. OSLER, WILLIAM: The principles and practice of medicine, 1892, Young J. Pentland, Edinburgh & London.
2. MACKENZIE, SIR JAMES: Diseases of the heart, 3rd Edition, 1913, Henry Frowde and Hodder & Stoughton, London.
3. BINGER, CARL: A critique of psychotherapy in arterial hypertension, New York Academy of Medicine Bulletin, 2nd series, 1945, xxi, 610.
4. BINGER, C. A. L., ACKERMAN, N. W., COHN, A. E., SCHROEDER, H. A., and STEELE, J. M.: Personality in arterial hypertension. Psychosomatic Medicine Monographs, 1945, Robert Brunner, New York.
5. ALLEN, F. M., and SHERRILL, J. W.: The treatment of arterial hypertension, Jr. Metab. Res., 1922, ii, 453.
6. HARRISON, T. R.: Personal communication, 1947.
7. SELYE, F. L.: Personal communication, 1947.
8. CORCORAN, A. R., and TAYLOR: Personal communication, 1947.
9. KEMPNER, W.: Treatment of kidney disease and hypertensive vascular disease with rice diet, North Carolina Med. Jr., 1944, v, 125.
10. ROWNTREE, L. G., and ADSON, A. W.: Bilateral lumbar sympathetic neurectomy in treatment of malignant hypertension, Jr. Am. Med. Assoc., 1925, lxxxv, 959.
11. SMITHWICK, R. H.: Technique for splanchnic resection for hypertension: preliminary report, Surgery, 1940, vii, 1.

# ATYPICAL FACE PAIN; A STATISTICAL CONSIDERATION OF 66 CASES \*

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HEADACHE and pain in the face are two difficult problems with which the practitioner of medicine must reckon. Unusual and irregular facial pain seems almost more of a therapeutic chore than the more familiar distress of headache.

## REVIEW OF THE LITERATURE AND CONSIDERATION OF TERMINOLOGY

Glaser<sup>1, 2, 3</sup> reviewed the problem with painstaking care in 1928, in 1938 and again in 1940. In 1928, 143 case histories from the Hospital of the University of Pennsylvania were studied critically and the complete syndrome of atypical face pain was presented for the first time and was called "atypical facial neuralgia." The records were analyzed from the standpoint of age at onset of symptoms, sex incidence, side involved, number of operations performed for relief, events coincident with the onset of distress, distribution and type of pain, agents used for the relief of pain, factors aggravating the pain and associated phenomena referable to the sympathetic nervous system. The author referred to the patients afflicted with this ailment as a pathetic lot and emphasized that no matter what course of treatment was pursued, the ultimate results were the same—dismal failure. In 1938, Glaser and Beerman<sup>2</sup> completely reviewed the literature to that date and cited the pioneer work of Sluder<sup>4</sup> and Cushing<sup>5</sup> and referred to the earlier reports of Fay,<sup>6, 7</sup> Davis and Pollock,<sup>8</sup> Wilson<sup>9</sup> and others. They presented 57 new cases which were added to their original 143. It was pointed out that Frazier and Russell<sup>10</sup> in 1924 had first used the term "atypical neuralgia" only for want of a better one. At the conclusion of this communication by Glaser and Beerman in 1938 it was stated:

"The term atypical neuralgia is not satisfactory but has been used to describe a peculiar, deep seated, aching pain that is not constant, not paroxysmal or intermittent, but marked by attacks of greater or less severity, occurring at varying intervals. Remissions are rare. Associated with this pain are sympathetic phenomena in 50 per cent of the cases. The pain does not follow the distribution of any of the cranial nerves and involves the scalp as well as the face." This, then, is the clinical problem to be considered in this report.

In 1940, Glaser<sup>3</sup> pointed out that significant additions had been made in

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the preceding 10 years to the knowledge of the sensory nerve supply of the face and progress has been made in the classification of the various clinical entities which could produce atypical face pain. In this review, while he still urged extreme caution in the carrying out of therapeutic measures, the note of pessimism sounded in the discourse in 1928 ("We have been absolutely nonplussed in our attempts to account for the origin of the pain phenomenon or to provide a remedy of any kind") had given way to a brighter note ("The pain need no longer be looked upon as incurable"). This transition to a more optimistic attitude regarding treatment and prognosis was, for the most part, due to his careful separation of the "secondary atypical neuralgias," the "neuralgias due to systemic diseases," and "neuralgias due to lesions of the head, chest and abdomen" from "primary atypical neuralgia." Glaser specifically referred to a group of cases which Brickner and Riley<sup>11</sup> designated as "autonomic faciocephalalgia" and cited three cases in which pain had been relieved when the patient received ergotamine tartrate and epinephrine. The striking component of the seizures which were relieved was the presence of symptoms definitely referable to the autonomic nervous system. Brickner and Riley quoted extensively from the publication of Vallery-Radot and Blamoutier<sup>12</sup> who described a case in which this component was present. They suggested that neither the term "atypical neuralgia" nor the term "atypical migraine" was proper and proposed the new term "autonomic faciocephalalgia," not for the purpose of applying a new term to an old syndrome, but as a means of getting away from old terms and conceptions which they felt to be misleading. Fay,<sup>13</sup> too, emphasized the need for thinking of these atypical neuralgias as either vascular neuralgias or definite nerve problems.

The thought was advanced by Glaser and Beerman in 1938 that all patients who have atypical facial pain should be given a trial of treatment with the various vasoconstrictor and vasodilator drugs. By this trial it might be possible to determine whether or not certain conditions might be removed from the perplexing group of primary atypical neuralgia. Such a course has been pursued at the Mayo Clinic in the section in which this study was made since 1936 in all cases of atypical facial pain.

Recent publications on this subject have been presented by Schreier,<sup>14</sup> Reichert,<sup>15</sup> Hyslop,<sup>16</sup> Martin,<sup>17</sup> Horton,<sup>18</sup> Gittins<sup>19</sup> and Walker.<sup>20</sup> The majority of these authors reviewed the literature and suggested certain medical or surgical procedures that have been attempted for relief of the pain. These procedures included division of the facial artery, vein and the accompanying sympathetic nerves,<sup>15</sup> blocking of the cervicothoracic portion of the chain of sympathetic nerves<sup>15</sup> and resection of the sphenopalatine ganglion.<sup>17</sup> They also referred to the now almost abandoned procedures of cervical sympathectomy and the stripping of the sympathetic plexus from the carotid trunk. Walker<sup>20</sup> questioned whether relief might not someday be offered some of these patients by prefrontal leukotomy.

No further consideration of the literature will be undertaken nor will the method of production of the pain be reviewed. Specialists in the field of neurophysiology, neurology and neurosurgery have described the method of production of pain in meticulous detail. Suffice it to say that the exact means of the conduction of pain in the obscure neuralgias of the head and face is a matter of some doubt. However, impressive evidence that multiple pathways may transmit such distress and that the vasculature, both arterial and venous, plays a significant rôle has been presented. Fay <sup>7, 13</sup> emphasized the rôle of the vasculature, and Davis and Pollock <sup>8</sup> studied particularly the part played by the sympathetic nervous system.

### STUDY OF 66 CASES

Our report will be concerned only with a statistical analysis of the case histories and a consideration of the therapeutic measures attempted in our section at the Mayo Clinic. Our primary purpose is to re-present the syndrome of atypical face pain and the records of 66 patients encountered in the section from January, 1940, to December, 1945, inclusive, have been analyzed carefully with this aim in mind. Four cases illustrative of the syndrome will be reported.

*Incidence.* Approximately 5,100 patients have been examined in the section in the course of six years. Sixty-six (1.29 per cent) of these were referred from the various general and special sections of the Mayo Clinic with a diagnosis of atypical face pain. The patients presented ailments which were not amenable to the more usual forms of treatment. The number of the patients studied in each of the years included in this review is as follows: 1940, six patients; 1941, twelve patients; 1942, thirteen patients; 1943, nine patients; 1944, eight patients; 1945, eighteen patients. Forty-six women and 20 men were observed. The distribution by sex is essentially the same as that in previous reports.

TABLE I  
Age Distribution at the Time of Admission and of Onset of Pain

Age	On Admission*			At Onset		
	Men	Women	Total	Men†	Women‡	Total
0 to 19	0	0	0	1	6	7
20 to 29	1	9	10	4	14	18
30 to 39	9	14	23	8	10	18
40 to 49	4	14	18	5	13	18
50 to 59	4	8	12	0	1	1
60 to 69	1	1	2	2	1	3
70 and above	1	0	1	0	0	0
Average	43.3	39.6	40.7	35.9	33.0	33.3

\* Youngest patient was 24 years old; oldest, 70 years old.

† Youngest man was 20 years old; oldest, 68.

‡ Youngest woman was 17 years old; oldest, 61.

*Age.* The age of patients at the time of their admission to the clinic, by decades, is given in table 1. The average age of the men at onset of symptoms was 35.9 years and of the women, 33.0 years. The man who was youngest at the time of onset was 20 years old and the oldest was 68 years old. The woman who was youngest at the onset of symptoms was 17 years old and the oldest, 61 years old. The average age at onset for both sexes was 33.3 years. Additional data are presented in table 1. Data concerning duration of symptoms are given in table 2.

TABLE II  
Duration of Pain

Years	Men	Women
0-1	6	8
2-3	2	7
4-5	4	13
6-10	3	11
11-15	3	1
16-20	1	5
21-30	1	0
31-40	0	1
Average, years	7.07	6.84
Shortest, months	7	2
Longest, years	27	35

*Occupations.* Five of the men were farmers, there were one each of the following: janitor, salesman, outdoor guide, lawyer, jeweler, optician, insurance agent, newspaper man, auto salesman, hotel manager, bartender, clerk, doctor and broker (investment and finance) and one was unemployed. The occupations of the women were as follows: Thirty-four were housewives; four, teachers and three, clerks. There was one each of the following: tax investigator, barmaid, registered nurse and beautician and one had no occupation.

*Marital Status and Information Concerning Families.* Sixteen of the 20 men were married and four, unmarried. Of the 46 women, 34 were married, one was divorced, three were widowed and eight had not married. Four of the married women had married for the second time and one of the widows had been married twice. Of the total group of 51 married patients 13 had no children. The problems of sterility, of sterility after the birth of one child and of one partner wanting a child or more children while the other did not seemed to occur more often than might be expected in such a small series. One patient had had an illegitimate child and an imbecile was born to one patient.

*Miscellaneous Information.* Neither the nativity of the patients nor their residence at the time of onset of the pain was considered to be of any significance. A careful review of the family histories revealed no significant information. None were stated to be relatives of the insane. No family history of trigeminal neuralgia or atypical face pain was given by any of the patients. No significant disease of the nervous system was present in the families of these patients according to the patients' records. A normal

complement of tuberculosis, diabetes, cancer and allergic disease was noted. One woman stated that one of her parents had had "a bleeding disease." No notation of a convulsive disorder in a relative was made in the records. Only a few references to migraine headache in the family histories were noted.

*Medical and Surgical Histories.* Medical histories were reviewed. Four patients had had gonorrhea and one had had syphilis which seemed of significant concern to him. One patient had had bronchiectasis. Two patients had suffered Bell's palsy in the year of onset on the side of the face subsequently plagued with pain.

An analysis of the surgical histories revealed the following data: Twenty patients had undergone appendectomy; five had undergone herniorrhaphy; four, cholecystectomy; four hemorrhoidectomy, and one each, thyroidectomy, gastric resection and transurethral prostatic resection. Two women had undergone perineal repair; six, hysterectomy; four, bilateral salpingectomy; five, unilateral oöphorectomy and two, bilateral oöphorectomy. The menstrual function had been halted in seven patients by these procedures but only two of the women had been castrated.

Twenty-three patients had undergone significant operations on the nose and paranasal sinuses. Tonsillectomy had been performed in 38 cases. The records do not state clearly in how many cases tonsils or adenoids or both had been removed for the relief of the facial pain, but such a procedure certainly had been carried out for this purpose in the majority of the cases. Although it was not recorded the vast majority of the patients had undergone

TABLE III  
Previous Neurosurgical Procedures

Procedures	Men*	Women†
Alcohol injection of the fifth cranial nerve	7‡	10
Procaine injection of the fifth cranial nerve	1	7§
Section of the fifth cranial nerve	1	6
"Pinching of the fifth cranial nerve"	1	
Pre-auricular block		1
Craniotomy. Gasserian neurectomy?	1	
Section of the infra-orbital and supra-orbital nerves	1	

[Note: Information was obtained from patients; hence, the neurosurgical terms are not precise. Operations on the fifth cranial nerve involved a peripheral branch in the majority of instances.]

\* Six men underwent 12 operations.

† Eighteen women underwent 24 operations.

‡ One patient had three injections.

§ One patient received three injections.

some dental operation in the course of their quest for relief of pain. In 36 cases attempts had been made to interrupt the pathways by which the pain was conducted (table 3). Fourteen of the 20 men and 28 of the 46 women had not undergone neurosurgical procedures.

*Weight.* The average weight of the men was 167 pounds (75.7 kg.). The maximal weight was 250 pounds (113.4 kg.) and the minimal weight, 119 pounds (54.0 kg.). The highest recorded weight of the women was



173 pounds (78.5 kg.) and the lowest, 101 pounds (45.8 kg.). The average was 132 pounds (59.9 kg.). Gross obesity or significant maldevelopment or malnutrition did not occur.

*Use of Alcohol and Tobacco.* The use of alcohol by these patients was noted. Only one case of near alcoholism was encountered. On a grading scale of 1 to 4 in which 1 represents the least and 4 the greatest consumption, the intake of the alcohol by three men was considered to be consumption, grade 1; three men, consumption, grade 2; five men, consumption, grade 3, and nine abstained from the use of alcohol. Thirty women stated that they were abstainers; consumption of alcohol by 15 women was graded 1 and for one woman consumption was graded 3. Applying the same scale to use of nicotine the results for men were as follows: no tobacco, four; grade 1, two; grade 2, eight; grade 3, five, and grade 4, one. The results for women re-

TABLE IV

Events Coincidental with or Related to (?) Onset of the Condition\*

Coincident Conditions or Related Events†	Men	Women
Dental operation	1	5
Sinusitis	3	1
Trauma		
Automobile accident	1	
Football accident	1	
Struck by jaijai ball	1	
Blow in face by husband		1
Operation on sinus	2	3
Influenza		3
Tonsillectomy		1
Vincent's angina	1	
Removal of cyst of jaw		1
Alcohol injection		1
Exposure during a snow storm		1
Thyroidectomy		1
Diagnosis of carcinoma of rectum		1

\* Information obtained from the patients' records.

† Ten men and 27 women stated that the pain was of spontaneous origin.

vealed that 28 did not smoke; consumption by seven was graded 1; of seven, graded 2, and of four, graded 3.

*Blood Pressure.* Study of determinations of blood pressure showed the average systolic blood pressure for the men was 124 mm. of mercury; the highest was 152 mm. and the lowest, 100 mm. of mercury. The average systolic blood pressure for the women was also 124 mm. of mercury; the highest was 170 mm. and the lowest, 95 mm. The average diastolic pressure for the men was 79.5 mm. with a high of 110 mm. and a low of 60 mm. and for the women the average diastolic pressure was 81.0 mm. with a high of 100 mm. and a low of 68 mm. Neither hypertension nor hypotension was a significant feature in these cases.

*Physical Examination.* The general physical examination of these patients was notably nonrevealing. A multitude of minor conditions, as would be found in any group of patients of similar age, was discovered. Five

women were definitely experiencing the menopausal syndrome and were receiving or recently had received treatment with estrogenic substances. No major physical aberration was noted in the group.

*Special Examinations and Laboratory Studies.* It may be stated at this point that in almost every case, special examinations were conducted by laryngologists, ophthalmologists, otorhinolaryngologists, neurologists and dental specialists at the clinic as part of the routine study of this condition. In the event that the patient had undergone previous neurosurgical procedures, the residual areas of anesthesia were noted and similarly, the evidence of previous dental operations or operations on the sinuses could always be seen. The rhinologists occasionally noted minor septal defects or thickening of the sinus membranes but on no occasion did they consider that significant disease of the nose or throat was present. On the few occasions that an electro-encephalogram was made, negative results were reported. Similarly, results of roentgenologic examination of the head, the face and other special structures were consistently negative and of no significance.

TABLE V  
Side of the Face Involved

	Left Side	Right Side	Both Sides	Alternating Sides
Men	11	6	2	1
Women	23	21	0	2
Total	34	27	2	3

Studies of blood chemistry, sedimentation rate, basal metabolic rate and urinalysis revealed no significant findings.

The average concentration of hemoglobin for the men was 14.7 gm. per 100 c.c. and for the women, 12.9 gm. The lowest recorded value for any patient was 11.0 gm. The patient was a woman. Significant anemia was not detected. The average leukocyte count for men was 9,000 and for women, 7,000. In two cases in which the patients were men, leukocytes numbered more than 9,000; in one, 12,500, and in another, 16,200. These high counts appeared to be of no significance. The flocculation test for syphilis gave negative results in all cases.

*Information Concerning the Pain.* Table 4 shows the events and conditions which patients felt were related to, or coincidental with, the onset of facial pain. The only events or conditions mentioned by more than one patient were infection of or operation on the paranasal sinuses, dental operation, trauma and postinfluenzal distress.

The only significant fact gained from consideration of the side of the face affected (table 5) is that our cases differ from those so conscientiously reviewed by Glaser. He pointed out that the involvement of the left side, the right side and both sides of the face occurs in essentially the same number of cases.

Table 6 shows the wide and irregular distribution of the pain. Apparently it is not distributed along established nerve pathways. It is readily seen that an explanation for such distribution of pain on a vascular basis

TABLE VI  
Location and Distribution of the Pain

Type of Distribution		Cases*
Individual region	Cheek (zygomatic region)	7
	Upper jaw (overlying ramus of mandible)	4
	Lower jaw (overlying body of mandible)	1
	Maxilla	1
	Infra-orbital region	1
	Total	14
Centered in cheek with distribution to one other region	Eye	2
	Nose	2
	Upper jaw	1
	Pre-auricular region	1
	Post-auricular region	1
	Total	7
Centered in cheek with distribution to two other regions	Supra-orbital region. Neck	1
	Eye. Temple	2
	Nose. Infra-orbital region	2
	Nose. Teeth	1
	Auricular region. Lower jaw	1
	Total	7
Centered in cheek with distribution to three other regions	Nose. Maxillary region. Upper jaw.	1
	Infra-orbital region. Eye. Temporal region.	1
	Nose. Temporal region. Auricular region.	1
	Temporal region. Supra-auricular region.	1
	Postauricular region	1
	Total	4
Centered in jaw with distribution to one other region	Upper jaw	2
	Temporal region	1
	Frontal region	1
	Lower jaw	1
	Chest	1
	Vertex of skull	1
	Total	6
Centered in jaw with distribution to two other regions	Occiput. Tragus of the ear	1
	Nose. Inside of mouth	1
	Infra-orbital region. Supra-orbital region	1
	Base of nose. Infra-orbital region	1
	Maxillary region. Supra-orbital region.	1
	Pre-auricular region. Infra-orbital region	1
	Maxillary region. Temporal region	1
	Total	7
Centered in jaw with distribution to three other regions	Cheek. Neck. Shoulder	1

\* Total cases, 46.

TABLE VII  
Duration of the Attacks of Pain

Duration of Pain	Men	Women
1 to 60 minutes	6	4
1 to 24 hours	5	5
1 to 7 days	4	8
Almost constant	1	5
Constant	3	20*
Data not available	1	4

\* One patient in this group obtained relief by taking codeine.

might be more consistent with the findings than an explanation on a neuro-genic basis.

Of the terms used by the patients in description of the distress the word "dull" was used 15 times; the word "ache" was also used 15 times. The specific expression "like a toothache" was used four times. The sense of "deep pain" was described by several patients and the impression was gathered in reviewing the records that this sensation was common to more than just several patients. A sense of "constancy" was attributed to the pain by nine patients. Sixteen described a pain component in addition to the more constant, dull ache. This additional element of distress consisted of occasional "sharp twinges" or "jabs" of pain. The word "severe" was used by eight patients and "excruciating" by four. Several patients at-

TABLE VIII  
Factors Which Relieved the Pain\*

Factor	Men†	Women
Heat	8	9
Cold		4
Moist cold		1
Warm dry climate		1
Summer	1	
Rest	3	
Diversion of interest		1
Pressure on eye	1	
Pressure on area of pain	1	
Pressure on great vessels of neck		2
Pressure on facial artery		1
Acetylsalicylic acid	3	7
Ephedrine	1	
Codeine		5
Morphine		3
Alcohol (by mouth)		3
Pentobarbital sodium		2
Atropine (intravenous)		1
Nicotinic acid		1
Preparation containing menthol		1
Hypodermic injection (probably not an opiate)	1	
Pregnancy		1
Swimming		1
Any neurologic procedure		1
Crying		1
Gum chewing		2
Data not available		9

\* Information taken from the history.

† Temporary remission for no apparent reason in seven cases.

tempted to describe a sense of weight or of pressure in the region where the pain occurred and several described the pain as "burning." Some of the more unusual descriptive words and phrases were: "an aching kind of numbness," "a severe, hard ache—a blank feeling," "like sharp files boring through the skin," "a burning pain associated with an alum and salty taste" and "a

TABLE IX  
Factors Which Accentuated the Pain\*

Factor	Men	Women
Heat		2
Cold	2	13
Cold drink		1
Dampness	1	1
Dry air	1	
Winter	3	1
Summer		1
Weather change	1	
Temperature change		1
Wind		1
Light		2
Sneezing	1	2
Coughing	1	1
Yawning		1
Crying		1
Facial movement		2
Wrinkling nose	1	
Washing face	1	2
Shaving	1	
Brushing teeth		1
Blowing nose		1
Exercise or effort	2	
Stooping		1
Standing		1
Lying down	1	
Sudden jolts of body	1	
Being awake	1	
Being asleep	1	
Weight of glasses		1
Local pressure	1	
Alcohol (by mouth)	3	4
Chocolate		1
Eggs		1
Milk		1
Menstruation		1
Nervousness	1	14
Fatigue		6
Time (midnight to 8 a.m.)		1
Almost everything		1
Nothing	1	
Data not available	4	13

\* Information taken from the history.

smooth pain with throbbing." Perhaps, as typical a descriptive phrase as any was "a dull, severe ache—unbearably throbbing at times."

In table 7 the duration of the attacks of pain is given. Twenty-three patients complained of constant pain and six of almost constant pain or a total of 29 patients with essentially constant distress. Twelve patients measured their attacks by days, 10 by hours and 10 by minutes. It will be observed that the duration of individual episodes of distress of the women seemed significantly longer than of the men.

The factors which offered relief to these patients are given in table 8. It will be noted that eight women had resorted to taking opiates whereas according to the records none of the men had. The multiplicity of measures offering relief to the women is also of interest.

Patients stated that numerous factors accentuated their facial distress (table 9). Again the multiplicity of measures mentioned by the women is

TABLE X  
Vascular Element

	Men	Women	Total
Present	5	11	16
Probably present	4	8	12
Probably absent	6	5	11
Absent	5	22	27
Total	20	46	66

impressive. Also, the obvious fact that emotional stress and nervous tension played significant rôles was recognized by 14 women and by none of the men.

We attempted to evaluate whether or not a vascular element was present in the distress of the individual patient (table 10). This is a highly personalized analysis and, as such, has a minimum of objective value. Such factors as the opinions of consultants who studied the patients, response to vasoconstricting and vasodilating drugs and the presence or absence of such phenomena of the sympathetic nervous system as lacrimation, rhinorrhea, hidrosis, hyperemia of the skin or conjunctiva, alterations in the size of the pupil and prominence of the blood vessels were considered.

TABLE XI  
Results of Treatment\*

Relief	Men	Women	Total
Complete	1	2	3
Significant	2	4	6
Moderate	3	7	10
Slight	3	3	6
No relief	9	25	34

\* No treatment was given to seven patients (two men and five women).

The presence or absence of the so-called functional factor in the background of these patients certainly deserves consideration. Of the 20 men, seven had a significant functional background for their complaint of pain in the face. Terms used by various consultants to describe these patients or their condition were "hypersensitive," "large functional element," "chronic nervous exhaustion," "neurogenic" and "psychogenic."

An element of psychoneurosis was thought to be present in 30 of the 46 cases in which the patients were women. The grading system in which 1

represents a mild and 4 a severe condition was used. Results were: grade 1, five patients; grade 2, fourteen; grade 3, eight; grade 4, three. Some of the terms used by the various consultants to describe the condition of these women included "functional," "early paranoic," "highly emotional," "unstable," "much tension" and "chronic nervous exhaustion." Whether or not such functional features preceded the pain in the face and were responsible for the production of pain in some measure or whether such features followed the long period of unrelieved pain is not known. It is barely possible that we have sought refuge in the comparative medical security of a diagnosis of functional disease when some obscure organic problem—vascular, neurogenic or otherwise—has escaped our attention.

*Differential Diagnosis.* The conditions most commonly considered in the differential diagnosis were: the major neuralgias of the head, face and neck; Paget's disease; Costen's temporomandibular syndrome; Sluder's sphenopalatine neuralgia; calculus in the submaxillary duct; disease of the nasolacrimal duct and diseases of the teeth and paranasal sinuses. A diagnosis of trigeminal neuralgia was not made in any case in this series. A section of the sensory root of the fifth cranial nerve was performed on one occasion and did relieve an associated paroxysmal, sharp component of the patient's distress but did not relieve the dull, throbbing ache which was the chief complaint. The "trigger-like" factors mentioned in table 9 were not particularly constant nor did they provoke a neuralgia-like pain. They were not the true trigger mechanisms noted in trigeminal neuralgia.

TABLE XII  
Treatment Which Gave Relief

Degree of Relief	Therapeutic Agents	Men	Women
Slight	Histamine (intravenously)	2	
	Histamine desensitization PT 9	1	2 1
Moderate	Histamine (intravenously)		1
	Histamine desensitization	2	2
	Histamine desensitization and benadryl (intravenously and orally)		1
	Histamine desensitization and thyroid extract PT 9		1
	D.H.E. 45 and saline Atropine (intravenously)	1	1 1
Significant	Histamine desensitization	2	1
	Histamine (intravenously), nicotinic acid, benadryl		1
	Histamine (intravenously), nicotinic acid; thyroid extract; adrenalin		1
	Adrenalin		1
Complete	Histamine desensitization		1
	Histamine desensitization, Kendall's cortical extract, nicotinic acid (intravenously)	1	
	Histamine desensitization, Kendall's cortical extract, PT 11		1

TABLE XIII

Therapeutic Agents Employed at the Clinic

- A. Histamine and histamine-like agents
  1. Histamine diphosphate (Abbott Laboratories)
  2. Hapamine (histamine-azoprotein, Parke, Davis & Company)
  3. The "PT" drugs (The Maltbie Chemical Company)
    - PT-8  $\beta$ (2-pyridyl) ethyldiethylamine hydrochloride
    - PT-9  $\beta$ (2-pyridyl) ethylmethylaniline hydrochloride
    - PT-10 1, (2-pyridyl) 2, (methylanilinopropane) hydrochloride
    - PT-11  $\beta$  (2-pyridyl) ethylaniline hydrochloride
- B. Antihistamine agents
  1. Benadryl ( $\beta$  dimethylaminoethyl benzhydryl ether hydrochloride, Parke, Davis & Company)
  2. Pyribenzamine hydrochloride (N'-pyridyl-N'-benzyl-N-dimethyl-ethylene diamine hydrochloride, Ciba Pharmaceutical Products, Inc.)
  3. Torantil (histaminase, Winthrop Chemical Company, Inc.)
- C. Hormones
  1. Estrogenic substance
  2. Androgenic substance
  3. Thyroid
  4. Kendall's adrenocortical extract
- D. Vitamins
  1. Vitamin A
  2. Vitamin C
  3. Vitamin B complex
  4. Nicotinic acid
  5. Thiamine
  6. Vitamin P
- E. Chemotherapeutic agents
  1. Sulfonamides
  2. Penicillin
- F. Anesthetic agents
  1. Procaine hydrochloride
  2. Alcohol
  3. Trichlorethylene
- G. Analgesic agents
  1. Acetylsalicylic acid
  2. Sodium salicylate
- H. Hypnotics and sedatives
  1. Barbiturates
  2. Dilantin sodium (diphenylhydantoin sodium)
- I. Parasympathetic agents
  1. Mecholyl chloride (acetyl- $\beta$ -methylcholine chloride)
- J. Parasympathetic depressants
  1. Atropine
  2. Tincture of belladonna
- K. Vasoconstrictor drugs
  1. Adrenalin
  2. Gynergen (ergotamine tartrate, Sandoz Chemical Works, Inc.)
  3. D.H.E. 45 (dihydroergotamine methanesulfonate, Sandoz Chemical Works, Inc.)
  4. Oxygen
- L. Miscellaneous agents
  1. Roentgen therapy
  2. Rosenow's vaccine
  3. Specific vaccine
- M. Placebo therapy

*Treatment.* Results of treatment in the section determined at the time the patient was dismissed are given in table 11. Three of the patients said that their pain had disappeared completely. In two of these three cases results of the "provocative test" in which histamine is injected subcutaneously were positive. The therapeutic agents used in the cases in which



some relief was obtained are listed in table 12. A complete listing of the therapeutic measures which we used is made in table 13.

### CASE REPORTS

*Case 1.* A married housewife, 26 years old, first came to the Mayo Clinic in March, 1945, with a complaint of pain in the right side of the upper jaw and right side of the lower jaw of eight years' duration. The pain apparently began spontaneously and then continued intermittently for the eight years preceding admission. Nine months before she was examined at the clinic the pain began to occur more frequently and to be more severe. Two months later she had all of her upper teeth removed. The pain was described as a constant aching soreness and burning, with occasional throbbing, of the right side of the upper jaw and right side of the lower jaw with occasional extension to the occiput and the tragus of the right ear. The pain sometimes felt like a "cold needle." A sharp, shooting, electric-shock component which lasted for only a few minutes accompanied the pain and occurred infrequently. The patient felt that, in some manner, this sharp pain was related to bowling, lifting and such exertional activity.

Many diagnoses had been made prior to admission of the patient to the clinic and these included trigeminal neuralgia, brain tumor, "cancer," "a maladjusted mandible" and dislocated vertebra of the neck. Many types of operation had been suggested.

The patient had been reared in a boarding home. Her parents had separated when she was four years old. She had had her tonsils removed in 1930. She had had pneumonia in 1920 and again in 1943. She related in a psychiatric interview that she had memories of an unhappy early childhood and that she frequently had been beaten severely by her father. She complained bitterly of the lack of parental affection. Her marriage had not been entirely happy. Sexual relations had never been satisfactory and the patient stated that she had a vigorous sexual appetite which was rarely satisfied. The patient had left her children for someone else to care for and had come to Rochester to live and to work until she received relief from the pain.

Physical examination revealed that the patient was an asthenic, weak and weary appearing woman of rather high intelligence. A papular eruption of indeterminate character was observed over the dorsum and the skin was described as "greasy." Results of general physical examination and routine laboratory studies were negative. No abnormalities were revealed on roentgenologic examination of the head, cervical portion of the spinal column and thorax. Study of the eyes, including funduscopy examination, study of the perimetric fields and refraction, special examination in the section on neurology, special examination of the ears, nose, throat and larynx and dental examination were made and all gave negative results.

The patient was treated in our section with various "vascular drugs" for six weeks. The following observations were made: 1. The intravenous administration of adrenalin invariably decreased the pain in the face but did not obliterate it completely. 2. The intravenous administration of histamine invariably made the pain worse. 3. When 150 to 200 mg. of benadryl<sup>21</sup> was given daily prior to the administration of histamine the customary response of pain to histamine did not occur.

By treatment with benadryl and histamine diphosphate we were able to keep the patient free of pain for 12 days. Our apparent success was terminated when the patient's husband came to visit her. When the patient was dismissed from our care the diagnosis was atypical face pain with definite vasodilating feature and a marked psychogenic element. The patient obtained no further relief from our therapeutic efforts.

*Case 2.* A woman, 44 years old, was examined in our section in February,

1942. Her complaint was of pain of two years' duration in the right side of the face. The family history was noncontributory. Marital history indicated that the patient was married for the first time in 1918 and was divorced after 11 years of marriage. In 1937 she married again. Past medical and surgical history revealed that the patient had undergone bilateral salpingectomy and tonsillectomy and had had typhoid fever, scarlet fever and influenza as a child.

The pain apparently had developed after the patient had had some teeth filled. In a subsequent attempt to relieve this pain, her dentist extracted two third molars and replaced all of her fillings. The pain was described by the patient as a severe ache not unlike that of a toothache which extended from the right side of her lower lip into the right side of her lower jaw and into the anterior part of the ear (not the canal). No trigger mechanisms were present. The inside of the mouth was not involved. The patient had had excellent medical care prior to her admission at the clinic. Procaine hydrochloride and alcohol had been injected in the sensory root of the right fifth cranial nerve on two occasions without relief. She also had received much medical treatment, including administration of estrogenic substance, large amounts of supplementary vitamins and calcium by mouth, heavy sedation and analgesia.

Physical examination revealed that the patient was a well-developed, well-nourished white woman whose face was slightly asymmetrical. The left orbital fissure was narrowed slightly. Her teeth contained many fillings. Some slight tenderness over the right temporal artery was present. Examination of the thorax, abdomen and pelvis, laboratory examination, including study of the urine and blood, roentgenologic examination of the head and thorax, examinations in the sections on otolaryngology, neurology, gynecology and dental surgery, examination of the eyes, including refraction, perimetric field study and funduscopy, and an electro-encephalogram were made and results were negative. Roentgenologic study of the cervical portion of the spinal column revealed localized hypertrophic changes in the fifth and sixth cervical vertebrae. The basal metabolic rate was normal. The ophthalmologist explained that the narrowing of the orbital fissure resulted from structural changes in the eyelids.

The patient was studied several times in the section, the last time in 1945. The ultimate result was total therapeutic failure. The patient, however, did contend that during three weeks in 1945 when benadryl was administered by mouth and histamine diphosphate by the intravenous route, she enjoyed the only period of freedom from pain which she had known since the onset. Unfortunately, this relief could not be maintained. No significant amelioration or exacerbation of the distress was obtained consistently with the use of either vasoconstricting or vasodilating drugs. The diagnosis when the patient was dismissed from the clinic was atypical face pain without vasodilating features. A marked functional element was thought to be present.

*Case 3.* A married woman, 51 years old, was admitted at the clinic in 1941. Her chief complaint was of pain in the left side of the face of three years' duration. The pain apparently followed the removal of a "small cyst of the jaw" by a dental surgeon. The patient had not been free of the pain since its onset.

A sister had migraine headaches. The patient had been married for 20 years, had had four miscarriages and one living child. The past medical history was not unusual. The patient had undergone right oöphorectomy. Subsequently laparotomy had been performed for intestinal obstruction. Operation on the right maxillary sinus had been performed some years previously. The patient related that some polyps had been removed.

The pain was described as a constant, dull, pulsating, drawing ache with a "burning and seething" quality in the left cheek bone with occasional paroxysms of

sharp, shooting pain spreading into the forehead and into the neck. The pain often occurred at night. This pain had become worse gradually. The paroxysms were brought on by chewing, talking and rubbing the face. Nothing had ever completely relieved the pain. Cold seemed to help slightly but the application of heat made the pain definitely worse.

Physical examination and complete laboratory studies of the blood and urine gave completely negative results. Roentgenologic examination of the head, cervical portion of the spinal column and thorax revealed no abnormalities. All of the physicians who examined the patient at the clinic doubted that she had trigeminal neuralgia. Subsequently this patient was admitted to the clinic eight times. Later in 1941 a deep injection of the sensory root of the fifth cranial nerve with alcohol was performed for diagnostic purposes and the patient gained significant relief. In 1942 the pain recurred and division of the posterior sensory root was suggested as a final resort for relief only of the sharp neuralgic pain. The patient chose to undergo this operation. The sharp pain was relieved, but the patient returned later with the same constant dull aching distress which had been her chief complaint prior to the neurologic operation. This patient was the only one in the series to undergo a neurosurgical operation other than local block for diagnostic purposes. In October, 1945, the patient returned contending that the pain was worse than it had ever been. On physical examination, a large, wide, elevated red streak in the skin was observed. The streak covered the middle portion of the left cheek and was definitely warm to the touch. The patient stated that this colored area perfectly indicated the region in which she suffered pain. The colored area was apparently present only when the pain was unusually severe. She had long complained of this color change, but it had never been observed at the clinic. The surface temperature of the red area in the left cheek was 32.9° C. (about 91° F.) and of the right cheek, 29.7° C. (about 85° F.), in a room in which the temperature was 25.6° C. (78° F.) and the humidity 40 per cent. This was checked several times and each time the left cheek definitely was 3° C. warmer than the right. Some lacrimation of the left eye and plugging of the left nostril was noted.

Intravenous administration of adrenalin did not eradicate the pain but did cause some of the redness to disappear. Intravenous administration of benadryl seemed to offer some relief of the pain in the cheek but this was certainly not complete. On a subsequent occasion the intravenous administration of benadryl when the redness was present seemed to offer approximately 80 per cent relief of pain. The patient contended that benadryl offered the most significant relief she had ever obtained.

The patient remained relatively pain-free for four months and then returned to the clinic with the same complaint after having failed to take the prescribed medication in any regular fashion. Treatment with histamine diphosphate (desensitization)<sup>22, 23</sup> and benadryl offered significant relief. Recently administration of pyribenzamine has kept this patient more comfortable than any previous medication.

*Case 4.* A woman, 40 years old, registered at the clinic in August, 1944. Her chief complaint was of intermittent pain in the left side of the face of two years' duration. The pain apparently began, after a severe attack of "flu," in the left side of the lower jaw and proceeded toward the vertex. The patient stated that she had refrained from going out at night into the cool air because if she did so the pain invariably developed. Occasionally this same distress occurred in the right cheek.

The past history and the family history were totally unrevealing. Complete laboratory studies of the blood and urine, including serologic tests, gave negative results. The provisional diagnosis was sphenopalatine ganglion neuralgia. The left middle turbinate (concha nasalis media) was enlarged and almost blocked the air passage. It was removed at the clinic. The patient obtained no relief from this operation.

Later it was possible for us to produce the facial distress by exposing the patient to the cold draft of an electric fan. Histamine desensitization was attempted for a long period but the attempt was not successful. The diagnosis when the patient was dismissed from the clinic the last time was atypical facial pain with a marked psychogenic element.

### COMMENT

Certain comments and interesting sidelights which have appeared in the literature regarding this troublesome syndrome are most deserving of repetition. Wilson<sup>9</sup> concluded that in some cases the condition was definitely psychogenic in origin and was based on deep, irreconcilable conflicts. He stated that "the face has become almost synonymous with the personality, . . . therefore, it is no wonder that shocks to the pride, long suppressed regrets and difficulties recognized but not allowed to reach the surface would cause a functional disturbance of this unit that could become a chronic source of irritation."

Fay,<sup>13</sup> as well as Glaser,<sup>1, 2, 3</sup> emphasized that every effort should be made to eliminate the secondary factors which may bring about the pain and that in those cases in which the pain has been present for a short time only, the results of treatment are far better than those in which the pain has persisted for a long time. Fay<sup>13</sup> also reemphasized the critical point that extreme caution must be observed in carrying out operative procedures on such structures as the teeth, the sinuses and the nervous system unless a pathologic process is definitely known to exist in these regions. Unwarranted assault on these structures almost invariably makes the patient's suffering more intense.

The need for a complete study of these patients with careful examination of all the special sense organs, roentgenologic study of the skull and careful neurologic and psychiatric study has been emphasized by Walker.<sup>20</sup>

Gittins,<sup>10</sup> in a paper concerning periodic headache and neuralgia with or without associated vasomotor symptoms, stated that, "Actually, just getting older accounts for the largest group of so-called 'cures,' regardless of whether or not there has been any treatment or even a diagnosis." He suggested that the reduction in the number of prospective victims is probably more a social than a medical problem.

Fay<sup>13</sup> pointed out that the three main difficulties in clarification of this problem are: (1) the variation in nomenclature, (2) the difficulty the patient has in describing his distress and (3) the variety of reports in the literature of small series of cases with varied treatment and poor or no follow-up data.

The general consensus in the literature seems to be that this syndrome is a manifestation of some structural or physiologic disturbance of the sympathetic nervous system which is either primary or secondary to some focal pathologic condition or is a manifestation of an underlying pain mechanism of the vascular system which may be distinct from the sympathetic nervous system.

## SUMMARY

We have submitted a brief review of the literature relevant to the syndrome of atypical facial neuralgia known by many other names in the literature and designated at the Mayo Clinic as atypical face pain. This term is preferred because it seems the most descriptive and, in the absence of specific knowledge as to the etiology of this condition, also seems most accurate. Interest has been manifest in this subject since the early contributions of Sluder (1908-1918).

We have attempted to re-present the syndrome as first described by Frazier and then completely described by Glaser. A statistical analysis of 66 consecutive cases encountered in six years has been presented.

The ratio of women to men was approximately 2:1. Similar ratios have been noted in other reports. The average age of patients at the onset of the pain was 33.3 years and the average duration was seven years.

The occupations of the patients were of no medical significance. A study of the marital status was of little assistance except to reveal 13 of the married patients were childless. The nativity, place of residence, family history and past medical history were of little note. No significant problems of obesity, underweight, hypertension, hypotension, alcoholism, major physical defects, anemia or leukocytosis were encountered in this series. Special laboratory studies of blood chemistry, urinalysis, roentgenologic studies, electro-encephalography and determinations of the basal metabolic rate were not enlightening.

The left side of the face was involved slightly more often than the right which was probably of no statistical significance. The distribution of the distress was widespread on the affected side. The descriptive terms used by the patients were mentioned and the concept that the sensation was a deep, dull, almost constant ache, often throbbing, was obtained. Twenty-eight patients had essentially constant distress. A significant number of dental operations, operations on the nose and paranasal sinuses and needless neurologic surgical procedures had been performed. A wide variety of agents and medications improvised by the patients or suggested by physicians elsewhere provided some relief and a similarly wide variety of factors accentuated the distress. Women stated that some 20 factors offered relief. They ranged from chewing gum, through pressure over the great vessels of the neck and face, to the use of opiates. Eight patients had at least some degree of addiction to the opiates.

Twenty-eight patients presented symptoms, in addition to the pain, which were highly suggestive of the presence of a vascular factor. These comprise about 42 per cent of the patients studied, a figure in substantial agreement with that given by Glaser for a much larger series.

The condition of 30 of the 46 women (approximately 65 per cent) and of seven of the 20 men (35 per cent) was thought to have a significant functional element.

Only nine patients obtained any significant relief and but three of these were relieved completely. The procedures which offered such relief are tabulated. A total listing of the preparations and procedures attempted in our section is given. The impression was obtained that the patients who had the most significant degree of vascular symptoms (that is, phenomena associated with the sympathetic nervous system) were more likely to obtain relief with treatment such as histamine desensitization or the use of vasoconstrictor medications. For example, two patients who obtained complete relief had been proved to be sensitive to histamine and the symptom complex had been reproduced with this agent, a process entirely akin to the well-established syndrome of histaminic cephalgia.

Study of this small series permits no conclusions. This communication serves only to reemphasize the difficulties in diagnosis and treatment and to contribute information concerning the condition. We are in complete agreement with the authors of recent medical articles who suggest that some of these cases of atypical pain in the face may represent a basic vascular problem and that the patient who has pain of obscure origin in the face and head deserves a trial of medication with vasodilating and vasoconstricting agents. It is a defect of our presentation that follow-up data are absent. We did not think that the results of treatment of a condition which is so difficult of description could be evaluated properly from a study of questionnaires. Consequently we elected to utilize the dismissal note on the patient's record and the patient's estimate of relief to determine whether improvement had occurred. We are well aware that the tendency in conditions of this type is for any new or different medication to offer at least transitory relief. For this reason, we wish to reemphasize that no claims are made for our therapeutic endeavors in this bizarre and mystifying problem. Certainly, any conservative management is deserving of trial and extended clinical study.

#### BIBLIOGRAPHY

1. GLASER, M. A.: Atypical neuralgia, so called: a critical analysis of 143 cases, *Arch. Neurol. and Psychiat.*, 1928, xx, 537-558.
2. GLASER, M. A., and BEERMAN, H. M.: Atypical facial neuralgia: an analysis of 200 cases, *Arch. Int. Med.*, 1938, lxi, 172-183.
3. GLASER, M. A.: Atypical facial neuralgia: diagnosis, cause and treatment, *Arch. Int. Med.*, 1940, lxxv, 340-367.
4. SLUDER, GREENFIELD: Concerning some headaches and eye disorders of nasal origin, 1918, C. V. Mosby Company, St. Louis, 272 pp.
5. CUSHING, HARVEY: The major trigeminal neuralgias and their surgical treatment based on experiences with 332 gasserian operations; the varieties of facial neuralgia, *Am. Jr. Med. Sci.*, 1920, clx, 157-184.
6. FAY, TEMPLE: Atypical neuralgia, *Arch. Neurol. and Psychiat.*, 1927, xviii, 309-313.
7. FAY, TEMPLE: Atypical facial neuralgia, a syndrome of vascular pain, *Ann. Otol., Rhin. and Laryn.*, 1932, xli, 1030-1062.
8. DAVIS, LOYAL, and POLLOCK, L. J.: The rôle of the sympathetic nervous system in the production of pain in the head, *Arch. Neurol. and Psychiat.*, 1932, xxvii, 282-293.

9. WILSON, D. C.: Atypical facial neuralgia, *Jr. Am. Med. Assoc.*, 1932, xcix, 813-816.
10. FRAZIER, C. H., and RUSSELL, ETHEL C.: Neuralgia of the face: an analysis of 754 cases with relation to pain and other sensory phenomena before and after operation, *Arch. Neurol. and Psychiat.*, 1924, xi, 557-563.
11. BRICKNER, R. M., and RILEY, H. A.: Autonomic facio-cephalgia, *Bull. Neurol. Inst. New York.*, 1935, iv, 422-431.
12. VALLERY-RADOT, PASTEUR and BLAMOUTIER, P.: Syndrome de vasodilatation hémicéphalique d'origine sympathique (hémicranie, hémihydrorrhée nasale, hémilarmoiment); (présentation de la malade), *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1925, ii, 1488-1493.
13. FAY, TEMPLE: Neuralgias of the face and head; their diagnosis and treatment, *Pennsylvania Med. Jr.*, 1941, xlv, 861-865.
14. SCHREIER, HERBERT: Trigeminal neuralgia-like syndrome; case report and treatment, *Med. Rec.*, 1940, cli, 359-360.
15. REICHERT, F. L.: Buccal neuralgia; a form of atypical facial neuralgia of sympathetic origin, *Arch. Surg.*, 1940, xli, 473-486.
16. HYSLOP, G. H.: Atypical facial neuralgia, *Laryngoscope*, 1941, li, 719-724.
17. MARTIN, R. C.: Atypical facial neuralgia, *Arch. Otolaryng.*, 1942, xxxv, 735-739.
18. HORTON, B. T.: Symposium: head and face pain, *Trans. Am. Acad. Ophth.*, 1944, xlix, 23-33.
19. GITTINS, T. R.: Headache and facial neuralgia (classification and differential diagnosis), *Trans. Am. Laryng., Rhin. and Otol. Soc.*, 1942, 191-201.
20. WALKER, A. E.: The relief of facial pain, *Med. Clin. North Am.*, 1945, xxix, 73-97.
21. MCELIN, T. W., and HORTON, B. T.: Clinical observations on the use of benadryl: a new antihistamine substance, *Proc. Staff Meet., Mayo Clin.*, 1945, xx, 417-429.
22. HORTON, B. T.: The use of histamine in the treatment of specific types of headaches, *Jr. Am. Med. Assoc.*, 1941, cxvi, 377-383.
23. HORTON, B. T., and MACY, DOROTHY, JR.: Treatment of headache, *Med. Clin. North Am.*, 1946, xxx, 811-831.

# STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS IN HUMANS

## I. MENINGITIS AND GENERALIZED HEMATOGENOUS TUBERCULOSIS \*

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### INTRODUCTION

SHORTLY after the first report on streptomycin by Waksman and his associates,<sup>1</sup> Feldman and Hinshaw observed that the drug exerted a pronounced effect upon the course of tuberculous infections in guinea pigs.<sup>2</sup> On the basis of these findings, a clinical investigation was started, and in September 1945 Hinshaw and Feldman reported that streptomycin exerted a suppressive effect upon the course of various forms of tuberculous infections in humans.<sup>3</sup> Although the therapeutic claims of these investigators were notably restrained in this and their subsequent reports,<sup>4, 5</sup> it was apparent that the alterations in the course of tuberculous infections observed by them were completely unprecedented.

As a result of these findings, an investigation of streptomycin in the treatment of tuberculous infections was initiated on the Cornell-New York Hospital Medical Service in January 1946. The present report is based on the observation of 17 patients with meningeal, miliary or other forms of generalized hematogenous tuberculosis who were treated during the first 18 months of the study. The results in 43 patients with pulmonary tuberculosis treated with streptomycin during the same period, are reported separately.<sup>6</sup>

### OUTLINE OF THE INVESTIGATION

*Preparation of Streptomycin.* A uniformly prepared and highly purified streptomycin sulfate was used. Its preparation and properties have been presented else-

\* Portions of this study were presented before the annual meetings of: the American College of Physicians, April 29, 1947; the American Society for Clinical Investigation, May 5, 1947; and the Section on Internal Medicine of the American Medical Association, June 12, 1947.

From the Department of Medicine of the New York Hospital-Cornell University Medical College.

The first part of this investigation was conducted under the direction of the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman. The subsequent investigation is a part of the Streptomycin Manufacturers-American Trudeau Society program which is being conducted in collaboration with the Tuberculosis Study Section of the National Institute of Health. The streptomycin was furnished by the Chemotherapeutic Committee; by a generous donation from Charles Pfizer and Company, Inc., Brooklyn; and from supplies donated to the American Trudeau Society by the Streptomycin Manufacturers.

The study was aided in part by grants from the National Institute of Health, and from the Lederle Laboratories, Inc., Pearl River, New York.



where.<sup>7</sup> The biologic potency of the final product coincided with the value for theoretically pure material, and is estimated to be at least 95 per cent pure. All of the material used was streptomycin A.<sup>8, 9</sup>

**Streptomycin Regimen.** A constant total daily dose of three grams of streptomycin administered intramuscularly in six or eight divided doses was used in all 12 of the adult patients. In the five children and infants, the dose was adjusted to body weight (20,000 micrograms per kilogram). In general, the total period of therapy was 120 days. Patients with meningitis received streptomycin intrathecally as well as by the intramuscular route. Individual doses of 0.1 to 0.375 gram (0.05 to 0.1 gram in infants) were administered at intervals ranging between 24 and 72 hours for total periods of 60 to 90 days. As evidence was soon obtained that individual doses of 0.2 to 0.375 gram were not always well tolerated,<sup>7, 10</sup> the 0.1 gram dose was not exceeded throughout the greater part of the investigation.

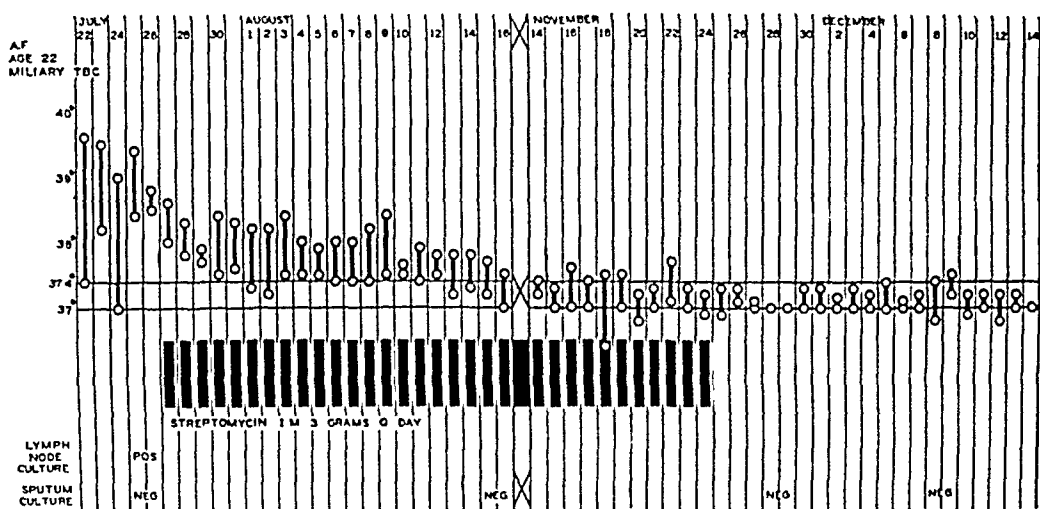


FIG. 1a Patient A. Fo, generalized military tuberculosis. Temperature chart showing daily range in degrees centigrade.

**Roentgenologic Studies.** Standard stereoscopic posterior-anterior exposures were made on every patient before treatment and at two-week intervals during the four months thereafter. Subsequent films were obtained at intervals of approximately one month. Lateral views were made whenever necessary.

**Skin Sensitivity to Tuberculo-protein.** The skin sensitivity to tuberculo-protein was tested before streptomycin treatment and at monthly intervals thereafter by the intracutaneous injection of appropriate dilutions of old tuberculin.

**Bacteriologic Studies.** Specimens of sputum (or other purulent exudates) were concentrated, digested with sodium hydroxide, and cultured on both the Tween\*-albumin medium of Dubos and Davis,<sup>11</sup> and egg-potato (Petragagni) medium, at two-week intervals during and subsequent to therapy. The particular Tween-albumin medium used contained 0.5 per cent albumin and 0.02 per cent Tween, and was incorporated into a solid medium with 1.5 per cent agar. When the presence of tubercle bacilli could not be demonstrated by culture of the sputum, gastric washings were obtained and similarly cultured. Pericardial, pleural, or cerebrospinal fluid and blood were cultured directly in the Tween-albumin liquid medium as well as on the Petragagni medium.

\* "Tween 80" is the trade name of the polyoxyethylene derivative of sorbitan monooleate, furnished through the courtesy of the Atlas Powder Company, Wilmington, Delaware.

*In Vitro Studies of Streptomycin Sensitivity.* The tubercle bacilli isolated from the patients before and at intervals after the institution of streptomycin therapy were tested in vitro for sensitivity to streptomycin in the following manner.

Five c.c. of the liquid medium (Tween 0.02 per cent—albumin 0.5 per cent, pH 7.0) which contains 500 mcm. of streptomycin per c.c. were pipetted into the first two

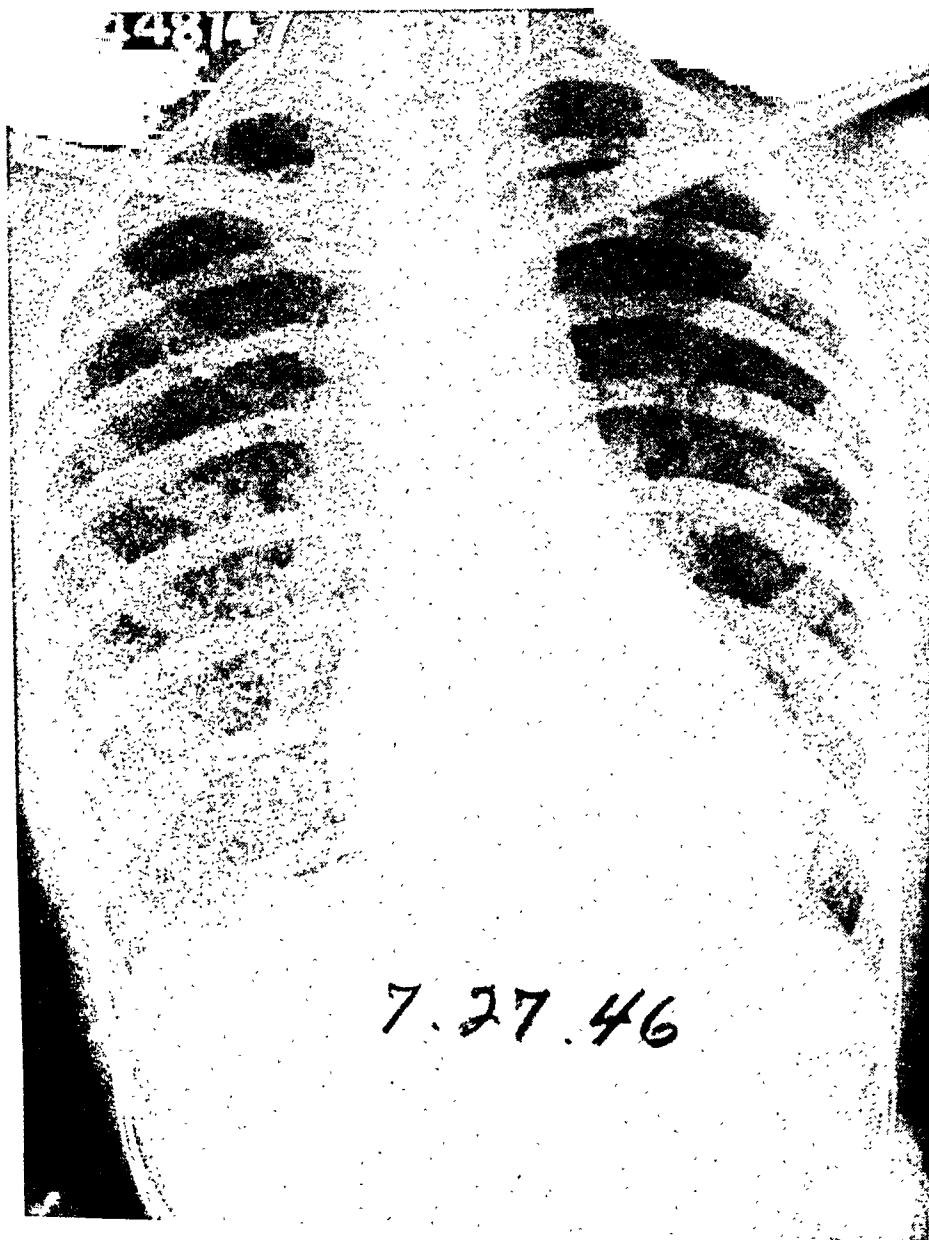


FIG. 1b. Patient A. Fo., chest roentgen-ray at start of streptomycin treatment. Note enlargement of cardiac shadow.

of a series of 10 tubes (six by one inch). An additional five c.c. of liquid medium were added to the second tube. Two-fold serial dilutions were then made, starting with the contents of the second tube and continuing throughout seven tubes. Thus, in the total of nine tubes the final concentrations of streptomycin ranged from 1.9 to 500 mcm. per c.c. Five c.c. of liquid medium which contained no streptomycin were

pipetted into the tenth tube which served as a control. The culture which was to be tested was grown for four to six days in the liquid Tween-albumin medium. The culture was first diluted with the liquid medium to a standard density, and 0.1 c.c. was inoculated into each of the 10 tubes. The cultures were incubated at 37° C., and were examined daily from the fourth to the seventh day after inoculation. The presence or

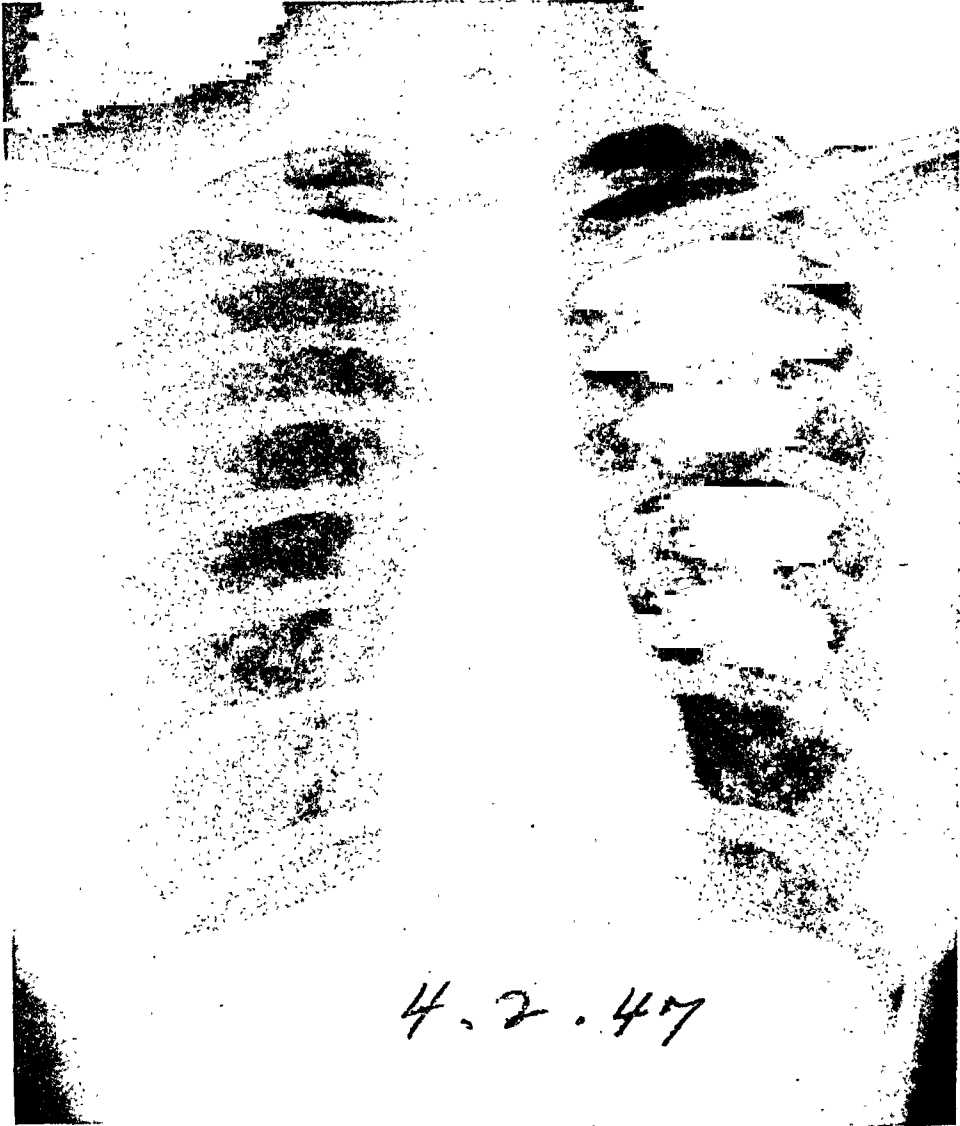


FIG. 1c. Patient A. Fo., chest roentgen-ray 8 months after start of 120 day course of streptomycin treatment. Note complete clearing of miliary infiltrations.

absence of growth was determined by gross inspection. The end-point was recorded in terms of the lowest concentration of streptomycin in which no growth was detectable on the seventh day of incubation. During the first half of the investigation, streptomycin concentrations higher and lower than the 500 to 1.9 mcg. per c.c. range were included in the test. It was found that no valuable information was obtained by the use of such concentrations, and that the test is more conveniently performed with the use of only ten tubes.

*Pharmacologic Studies.* The concentrations of streptomycin in the various body fluids and exudates were determined by the bioassay method of Stebbins and Robinson<sup>12</sup> and by the chemical technic of Boxer and Jelinek.<sup>13</sup> In order to investigate the toxicity of the highly purified streptomycin on long-continued administration, the function (and histopathologic changes) of a number of organs and systems were studied by appropriate technics. The results of these studies have been published elsewhere.<sup>7, 10, 14</sup>

## OBSERVATIONS AND RESULTS

*Tuberculous Meningitis.* Nine patients with bacteriologically proved tuberculous meningitis have been treated with streptomycin. In seven, the meningitis arose as a complication of acute miliary tuberculosis and all seven have died. The remaining two, neither of whom had miliary tuberculosis, have been in remission for five months since the cessation of therapy.

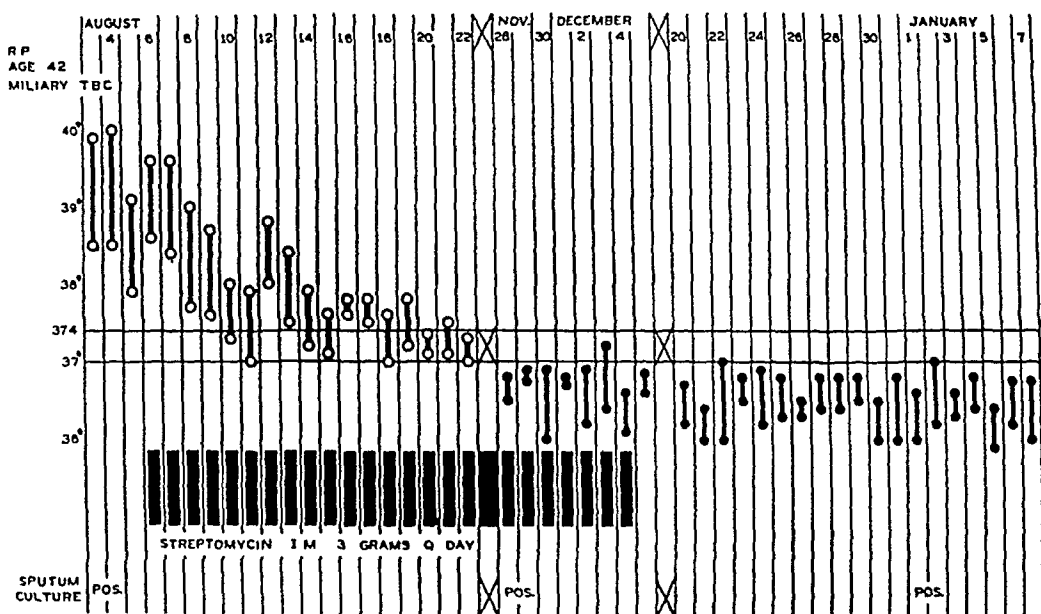


FIG. 2a. Patient R. Ph., generalized miliary tuberculosis which developed in course of chronic pulmonary tuberculosis. Temperature chart.

Only four of the nine patients presented the characteristic clinical picture of acute tuberculous meningitis at any time during the course of the infection. In the other five, all of whom have died, the meningitis ran a subacute or asymptomatic course in an illness which was dominated by the manifestations of acute miliary tuberculosis. The two types will be considered separately.

*Clinically Evident Tuberculous Meningitis.* At the time streptomycin therapy was started, all of the four patients with clinical meningitis were acutely ill with high fever and nuchal rigidity. One was in deep coma, another was stuporous, and the remaining two were irrational. Symptoms suggestive of meningitis had been present for one to four weeks before the institution of antimicrobial therapy.

The patient in coma, a two year old infant with previous miliary tuberculosis, never regained consciousness although she survived three and a half months after the start of therapy. Tubercle bacilli could not be cultured

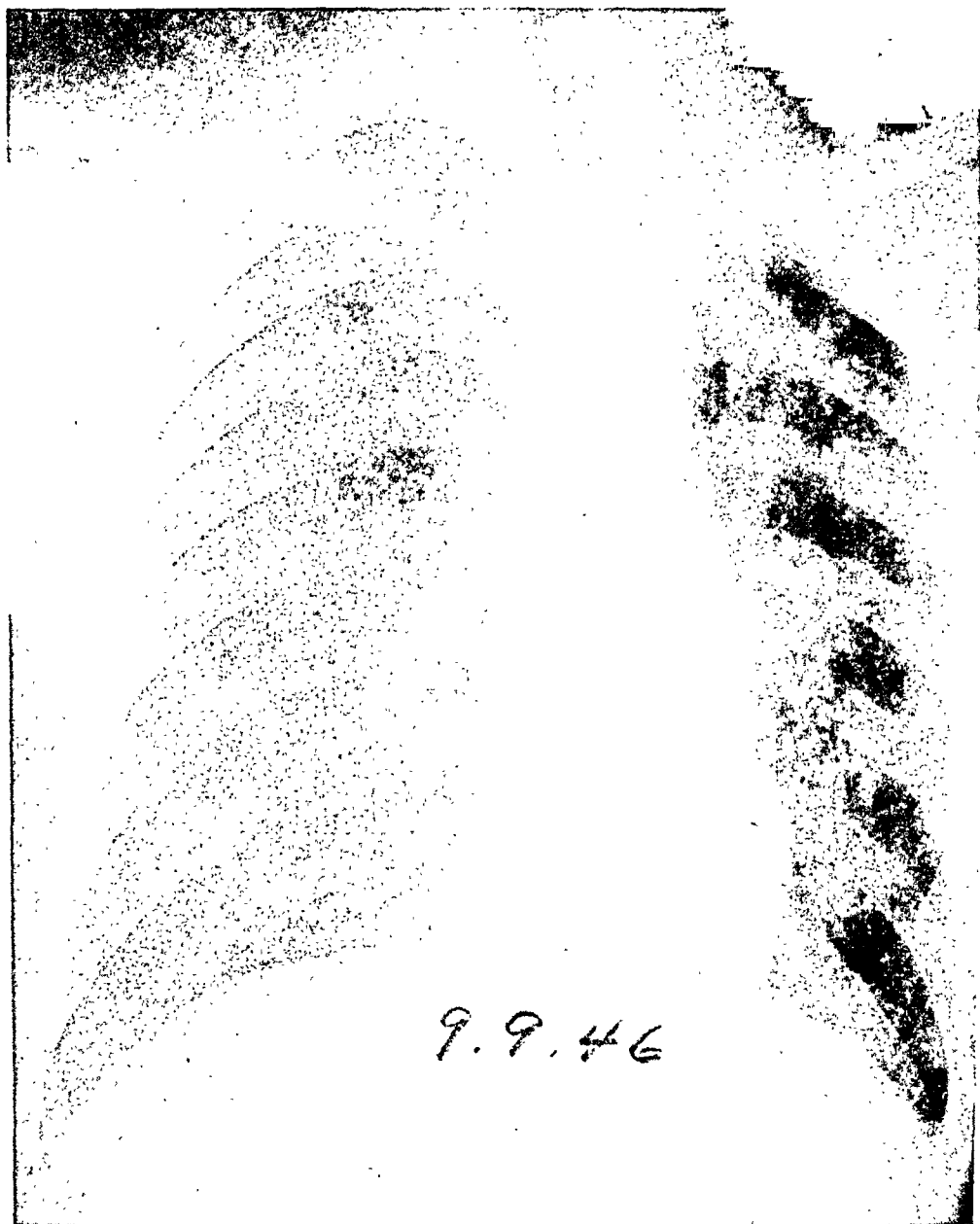


FIG. 2b. Patient R. Ph., chest roentgen-ray at start of streptomycin. Note left apical cavity unclosed by thoracoplasty which had been left incomplete because of ipsi-lateral bronchogenic spread. Disseminated hematogenous miliary infiltrations well seen in contra-lateral lung.

from the cerebrospinal fluid after the seventeenth day of therapy, and cultures of the brain and cerebrospinal fluid at autopsy were sterile. Death occurred as a consequence of internal hydrocephalus, and only a few tiny areas of

meningeal inflammation were demonstrable on microscopic examination of the tissues. Although it appeared that the streptomycin had exerted a considerable effect upon the course of the meningeal infection, the central

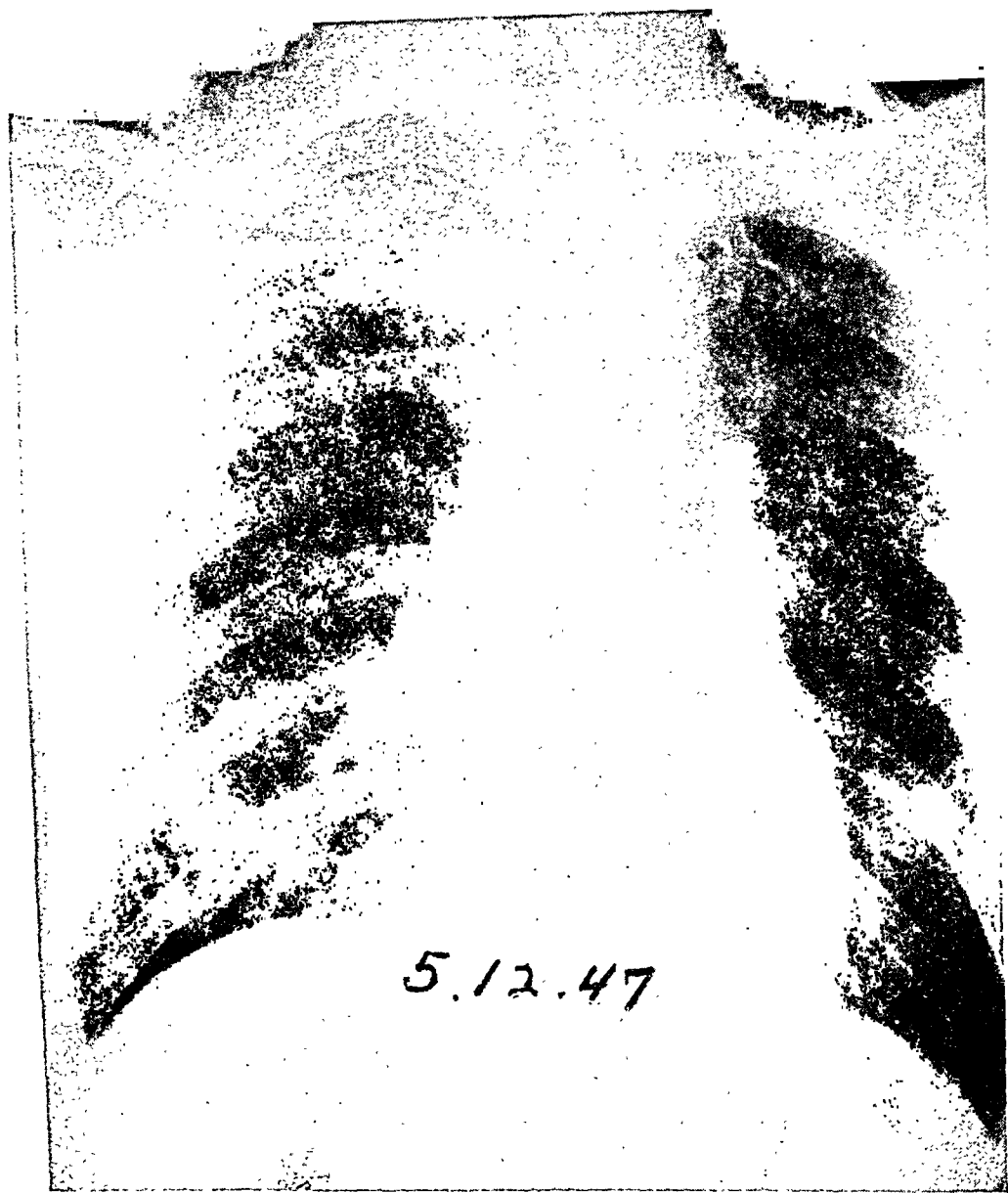


FIG. 2c. Patient R. Ph., chest roentgen-ray 9 months after start of 120 day course of streptomycin. Note closure of cavity, conspicuous regression of bronchogenic infiltrations, and disappearance of miliary infiltrations.

nervous system presumably had been damaged before treatment to an extent which precluded ultimate recovery.

The other patients with obvious meningitis included a 63 year old man with associated miliary tuberculosis and two 19 year old women with no evidence of generalized hematogenous dissemination. They showed con-

siderable improvement during the first seven to 10 days of streptomycin which was administered both intrathecally and intramuscularly.

Improvement consisted of a decline in fever within three to five days of the start of therapy and an appreciable decline in nuchal rigidity so that it

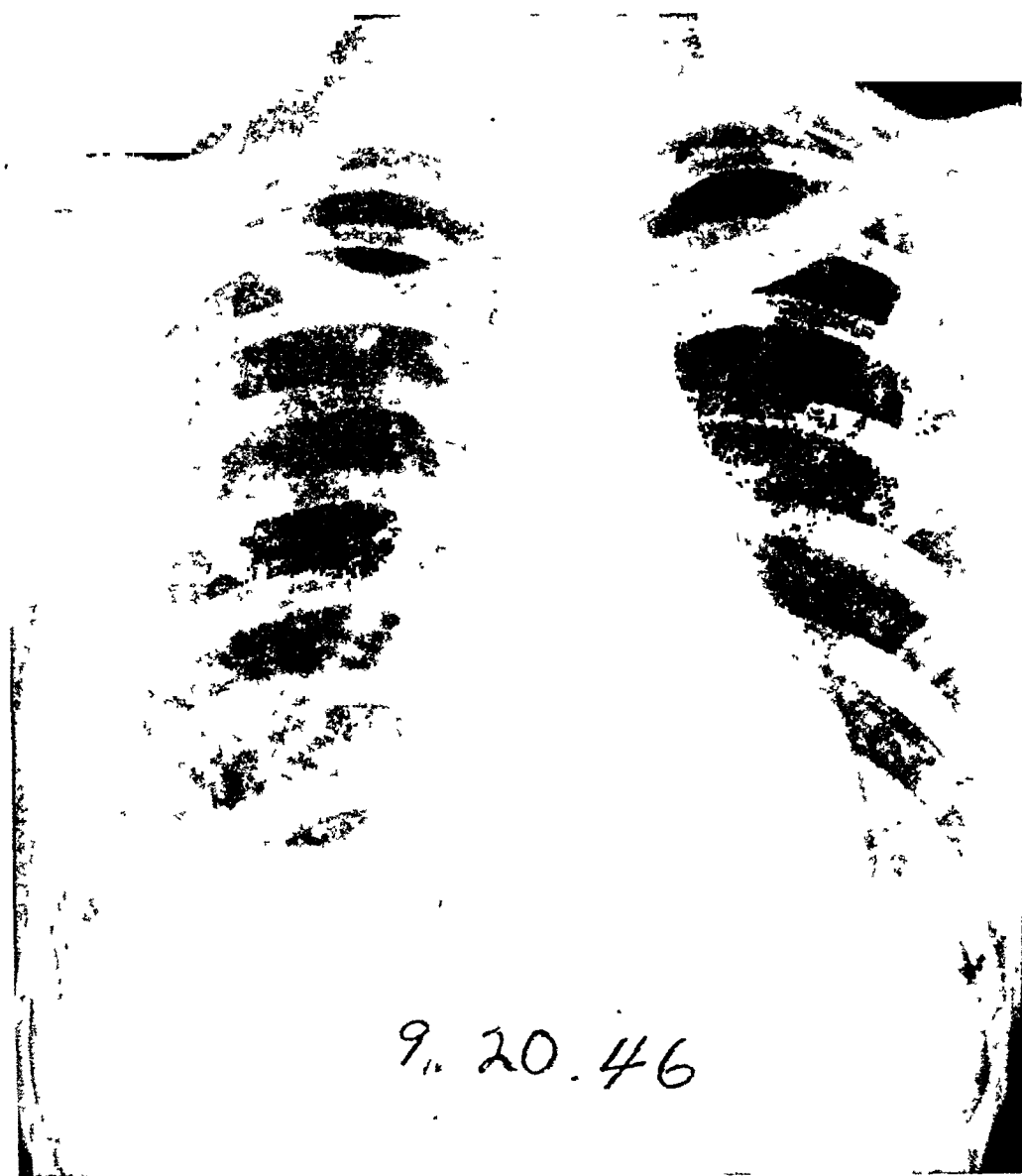


FIG. 3a. Patient R. Sc., case of acute generalized miliary tuberculosis transformed into chronic infection with residual activity in scattered foci. Chest roentgen-ray at start of treatment. Note relatively large size of "miliary" infiltrations.

was only barely detectable at the end of the first week. The two irrational patients became much more alert and the patient who had been stuporous regained consciousness. Subsequent to the first seven to 10 days of therapy daily variations in the status of the meningitis were no longer perceptible.

The patients presented the picture of a subacute or chronic illness. Fever (37 to 38.5° C.) continued, and the principal symptoms (headache, backache, leg pains) could be attributed with equal likelihood to either the disease or the intrathecally administered streptomycin.

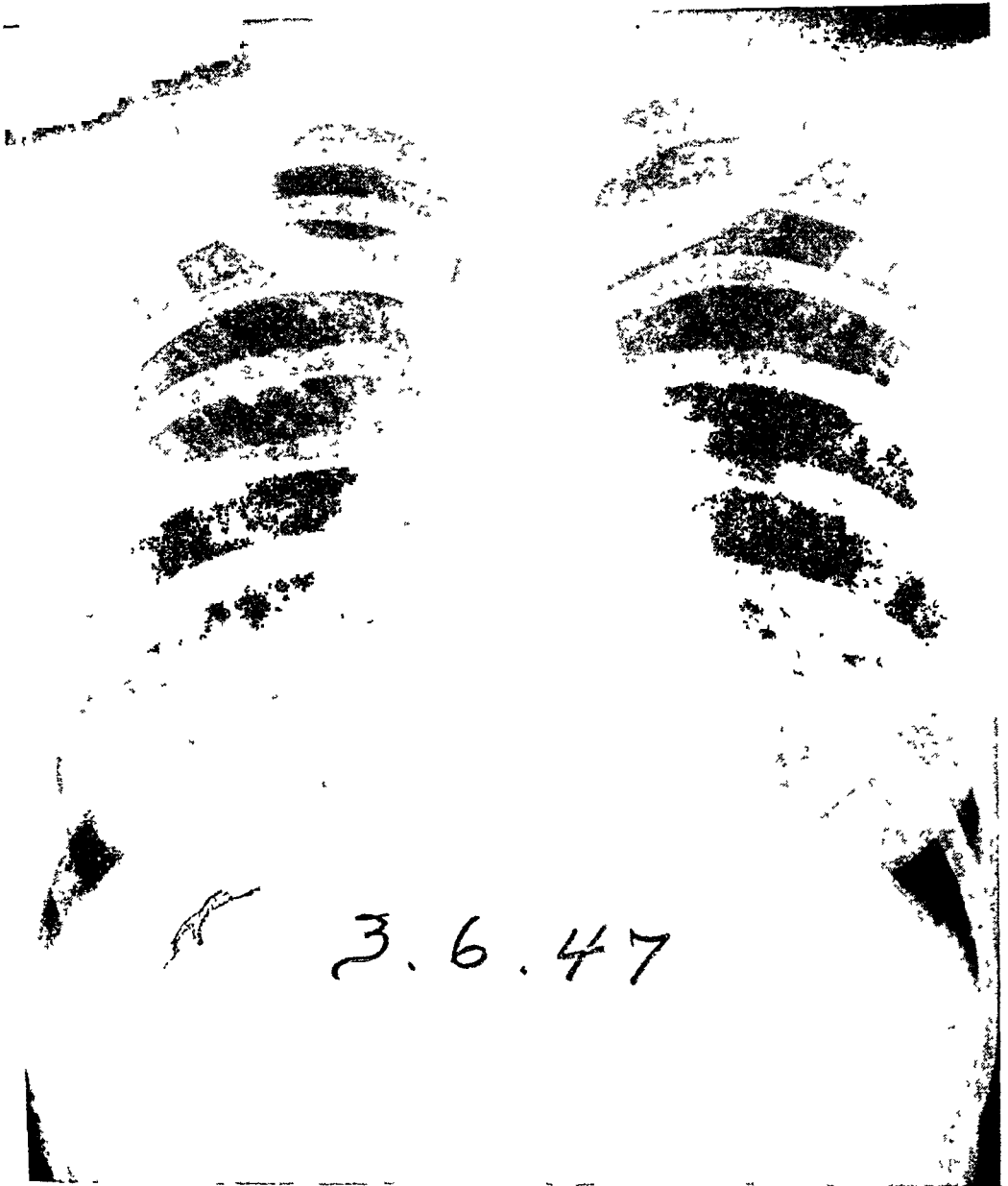


FIG. 3b. Patient R. Sc., five and one-half months after start of treatment.

The subacute illness, without appreciable daily change, persisted for approximately one month. The 63 year old man died suddenly on the thirty-ninth day of treatment. Postmortem examination revealed an extensive purulent meningitis involving the spinal cord, and minimal evidences of meningitis over the base of the brain.



The two young women, neither of whom had miliary tuberculosis, continued to present the same clinical picture of subacute illness during the second and the third months of treatment. Although they did not appear acutely or dangerously ill, there was no tangible indication that they would recover. During the fourth month of streptomycin therapy, when the

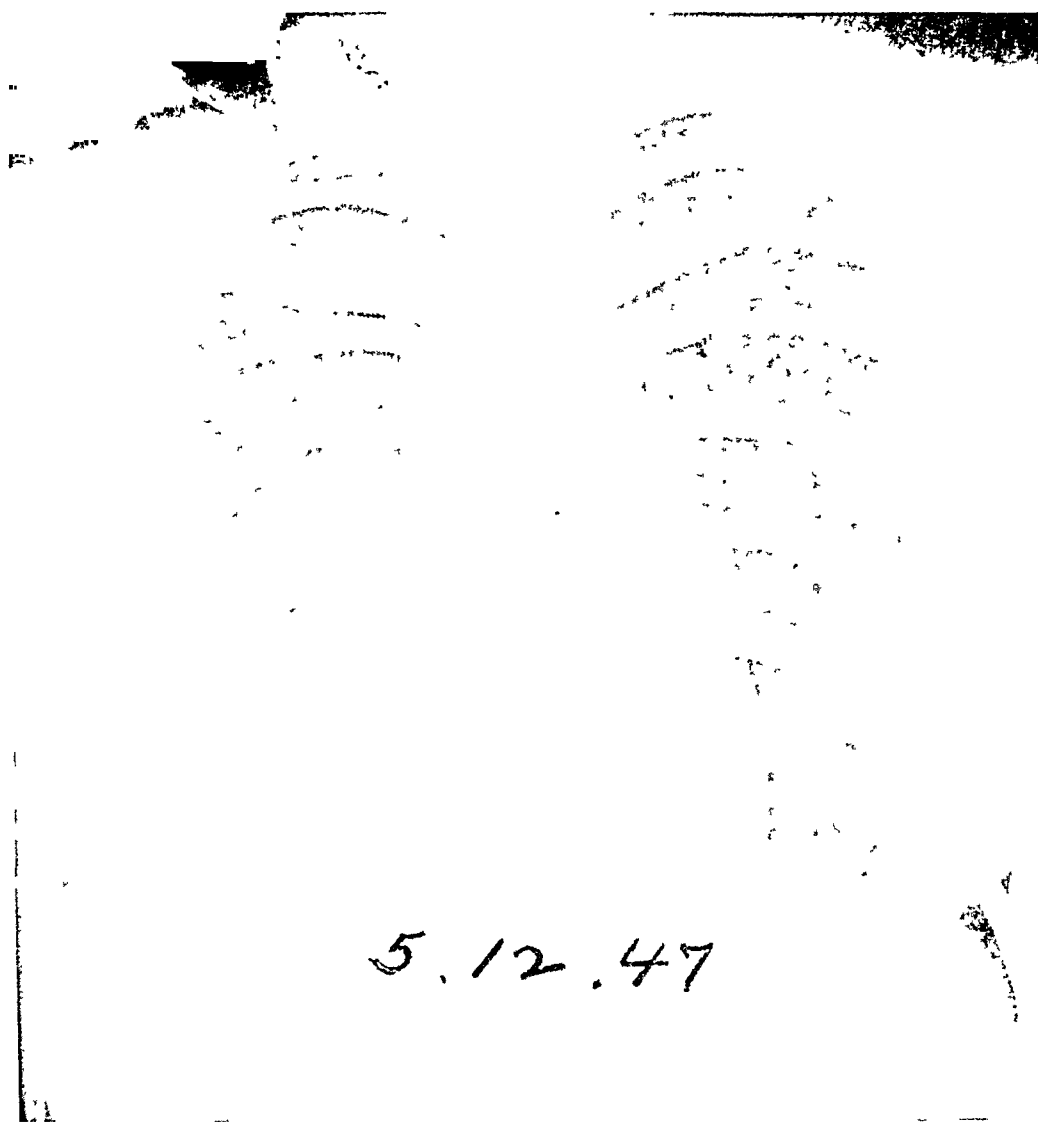


FIG. 3c. Patient R. Sc., nearly eight months after start of treatment. Except for a pleural haze in the right lower lung field, resulting from an intervening pleurisy, the picture is not appreciably changed.

intrathecal administration of the drug had been discontinued, improvement was apparent and the patients became virtually asymptomatic.

Five months after the cessation of streptomycin therapy, these two young women show no signs of meningitis, present no evidence of mental impairment, and have normal cerebrospinal fluids save for protein concentrations

of 68 and 75 mg. per cent. One patient has been totally deaf since the fifth week of therapy. This phenomenon may represent a sequel of the infection or may have resulted from streptomycin toxicity.<sup>7, 10, 14</sup> The other patient is under care for tuberculosis of the spine which was discovered after, but probably antedated, the onset of the meningitis.

*Subacute or Asymptomatic Tuberculous Meningitis.* Six of the nine patients had acute miliary tuberculosis but did not present the characteristic clinical picture of meningitis at the time streptomycin therapy was started. One of them was the infant already described, whose clinically characteristic meningitis occurred as a late relapse of a previous meningeal infection. In one of the six the cerebrospinal fluid was not examined prior to therapy.

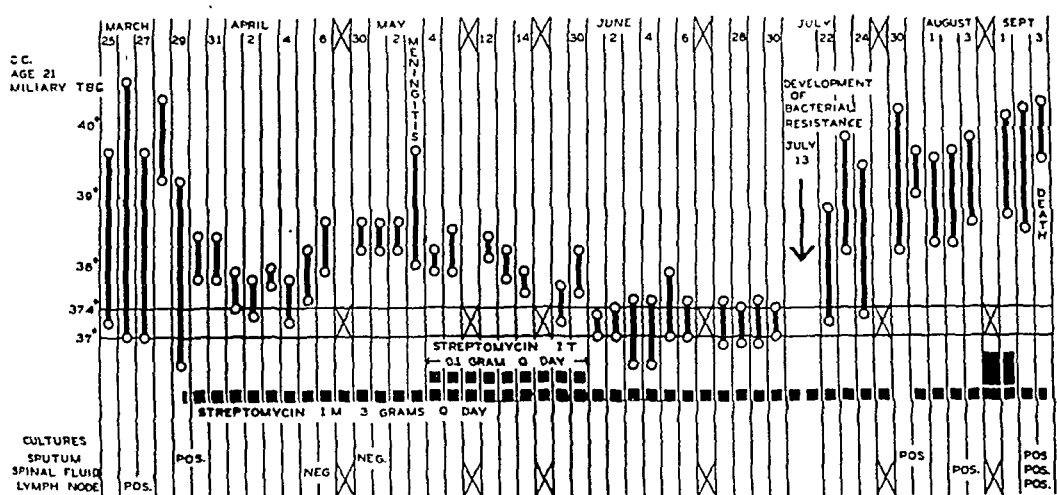


FIG. 4a. Patient C. Co., generalized miliary tuberculosis illustrating diphasic course with relapse despite uninterrupted treatment. Temperature course. Note recurrence of fever after development of bacterial resistance.

In only two of the others was the pre-treatment cerebrospinal fluid shown to be abnormal. Both received streptomycin intrathecally as well as intramuscularly at the start of antimicrobial therapy. The remaining four patients received no streptomycin intrathecally until meningeal involvement became evident. It should be noted that this complication did not appear until after 35 to 96 days of streptomycin therapy.

The first indication of meningeal disease was a relatively sudden increase or return of fever at a time when the miliary tuberculosis appeared to be receding under therapy. The rise in temperature was accompanied by slight headache but all other clinical evidences of neurologic disease were lacking. Cerebrospinal fluid examinations revealed characteristic abnormalities of meningitis.

The addition of intrathecally administered streptomycin to the therapeutic regimen was usually followed by reduction in fever and disappearance of headache. During the first month of intrathecal therapy, the clinical course was essentially the same as that observed in the same period in the patients

with frank clinical meningitis. Two attained temporary remissions of the meningitis. One of them remained completely well physically and mentally for a six week period during which she received no antimicrobial therapy. Her remission was followed, however, by clinically evident and eventually fatal meningitis. It is worthy of note that in this group, hers was the

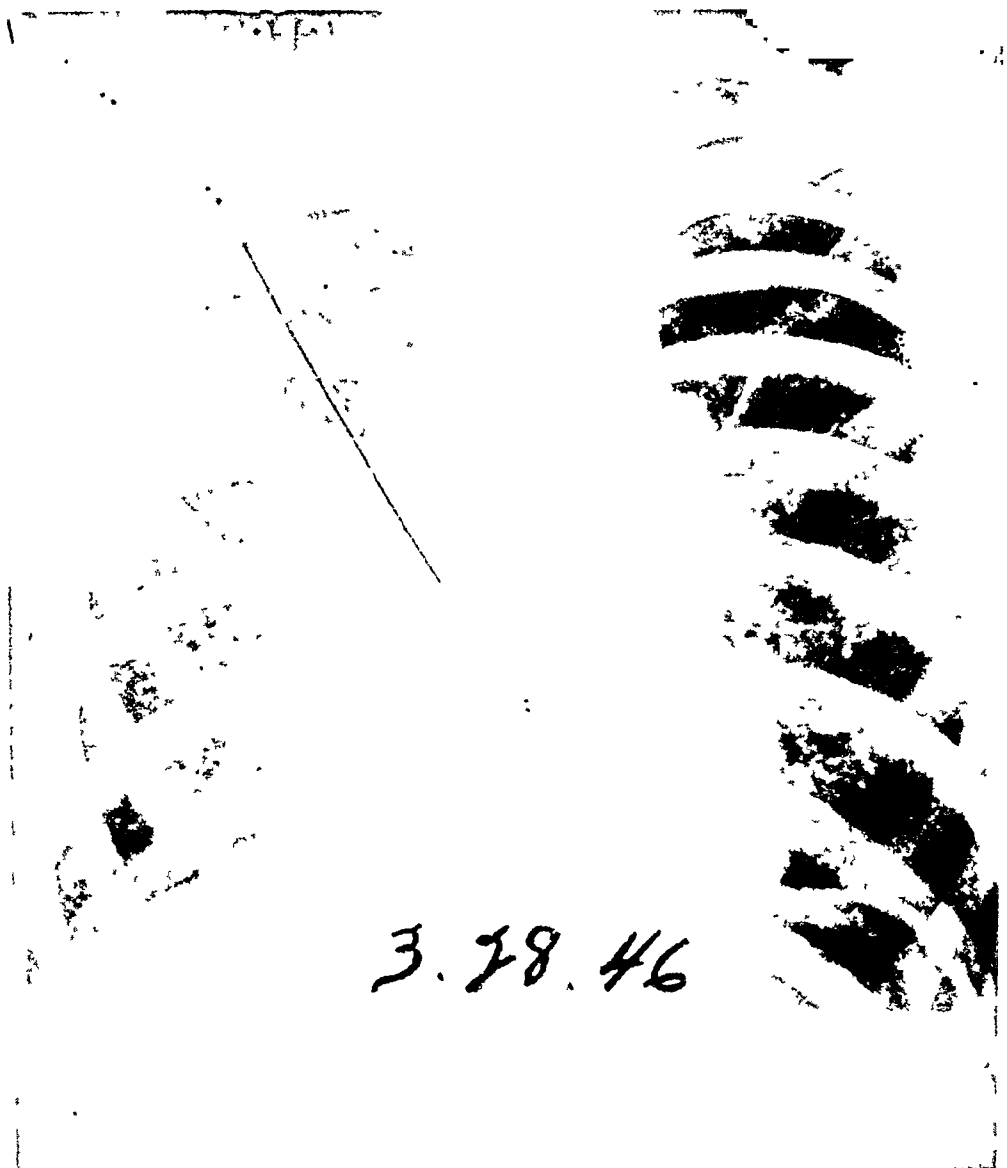


FIG 4b Patient C Co, roentgen-ray of chest before start of streptomycin treatment.

only death which was clearly attributable to meningitis. The second patient remained free of clinical evidence of meningitis but an increased cerebrospinal fluid protein persisted for a period of three months after the cessation of the intrathecally administered streptomycin. Death in this instance, as well as in the other patients of the group, apparently resulted from relapsing strepto-

mycin-resistant generalized hematogenous tuberculosis and not as a consequence of meningitis. In all the fatalities, however, bacteriologic evidence of the persistence of the meningitis was present at death.

The duration of life from the first evidence of meningitis to death or relapse ranged from 20 to 124 days in this group of six patients with subacute meningitis associated with miliary tuberculosis.

*Cerebrospinal Fluid Abnormalities.* The course of the cerebrospinal fluid abnormalities before, during and after treatment is presented in table 1, where it may be seen that before the intrathecal administration of streptomycin was started, the cerebrospinal fluid findings were those usually encountered in tuberculous meningitis. In addition to the presence of *M. tuberculosis*, the concentrations of sugar were abnormally low (10 to 46 mg. per cent) and the values for total protein and the numbers of cells were appreciably elevated. In general, there was no conspicuous alteration in the amount of chlorides. It is worthy of note that in one patient, tubercle bacilli were cultured from the cerebrospinal fluid when the only other abnormality was an increase in protein (73 mg. per cent). After one month of intramuscularly administered streptomycin, she had developed no clinical manifestations of meningitis, but the values for sugar, cells and total protein had become distinctly abnormal.

TABLE I  
Cerebrospinal Fluid Findings before, during and after Treatment in  
Nine Patients with Tuberculous Meningitis

Name	Pressure			Cells			Sugar			Protein			Cultures		
	Be- fore	During	After	Be- fore	During	After	Be- fore	Dur- ing	After	Be- fore	During	After	Be- fore	During	After
C. Co.	130	90-130	190	175	9-150	3	46	47-93	60	39	30-72	51	neg.	neg.	+
R. He.	Inc.	Inc.	N.	45	40-1100	312	28	26-62	55	—	115-1125	250	+	neg.	neg.
S. Le.	150	85-150	—	222	30-340	5	43	43-93	103	30	26-116	30	+	+	+
P. Bu.	N.	N.	Inc.	900	90-1300	14	32	16-47	34	73	70-1010	79	+	+neg.	neg.
	N.	—	—	415	50-900	—	25	16-76	—	105	76-167	—	+	+neg.	neg.
G. Te.*	100	150	—	60	260	—	29	19	—	82	92	—	+	+	+
A. Ke.	175	50-160	—	44	20-350	—	10	35-71	—	131	80-394	—	+	+	+
E. De.	175	40-200	—	109	45-245	—	33	32-74	—	91	80-285	—	+	+	+
C. Sn.	500	140-650	120	146	66-400	10	10	23-50	55	108	75-443	55	+	0	0
H. Ra.	700	150-300	100	325	30-333	15	20	29-52	50	280	180-403	78	+	0	0

\* Treated 3 days only.

Inc. = Increased.

N. = Normal.

In the entire group, the principal changes in the cerebrospinal fluid after the start of intrathecal therapy consisted of the disappearance of the positive cultures for tubercle bacilli and a gradual increase in the concentration of sugar.

The values for cerebrospinal fluid sugar gradually increased during the first week of intrathecal therapy in five of the patients in whom the sugar was low before therapy. In one, however, the concentration of sugar was not consistently above 40 mg. per cent until after 120 days of treatment.

The cerebrospinal fluid sugars of the others, all of whom had subacute meningitis in association with miliary tuberculosis, remained within the normal range until death.

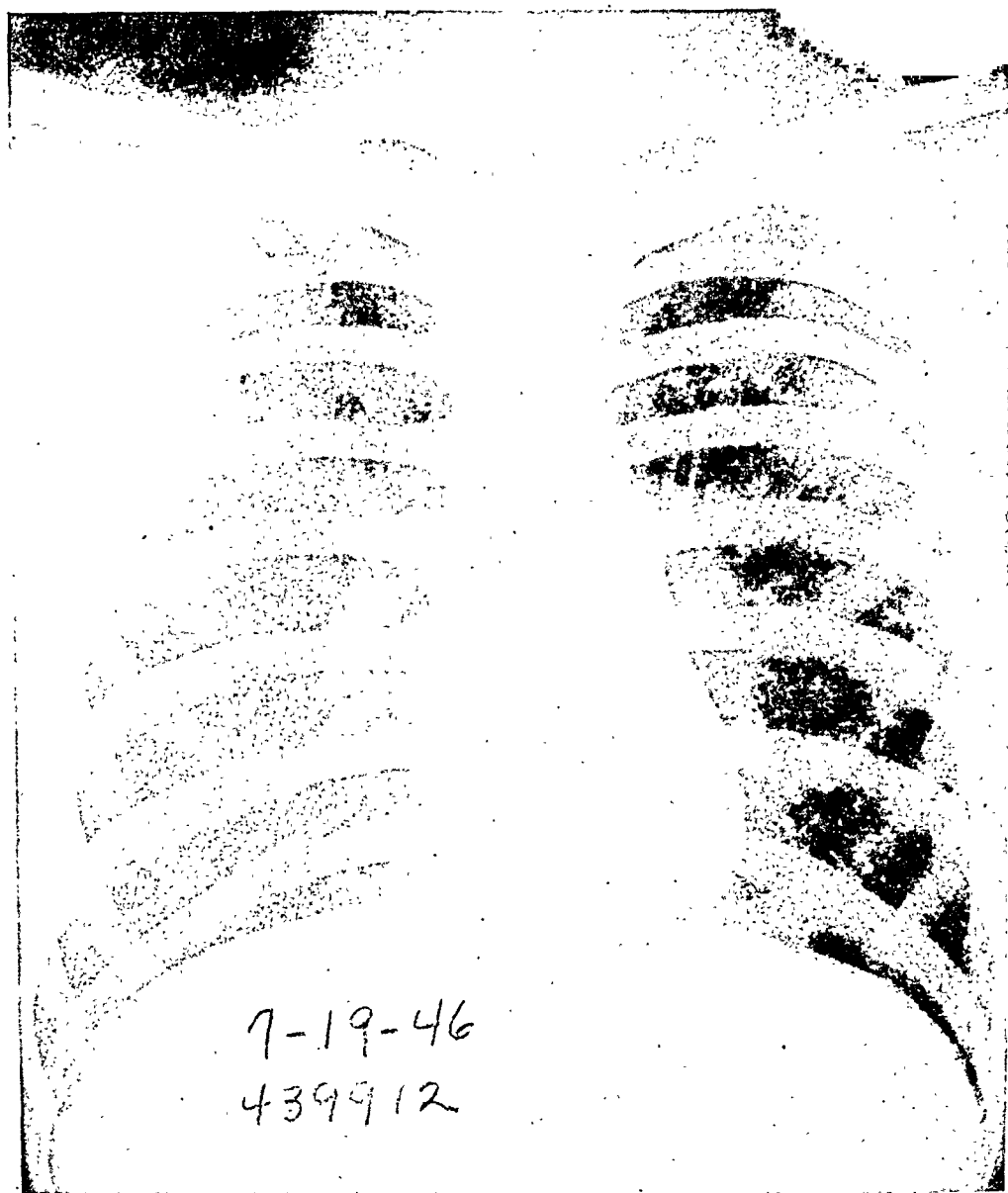


FIG. 4c. Patient C. Co., roentgen-ray of chest just prior to onset of relapse. Note complete clearing of miliary infiltrations and regressions of mediastinal lymph node enlargement.

Except for abnormalities in the quantity of sugar and the presence or absence of organisms, determinations of the various components of the cerebrospinal fluid yielded little information of value during the period of therapy by the intrathecal route. Irrespective of the eventual outcome, the total number of cells and the total quantity of protein remained elevated so long

as the intraspinal treatment was continued. When intrathecal administration was discontinued, the number of cells fell rapidly to within or slightly above the normal range. The diminution in protein, however, was appreciable.

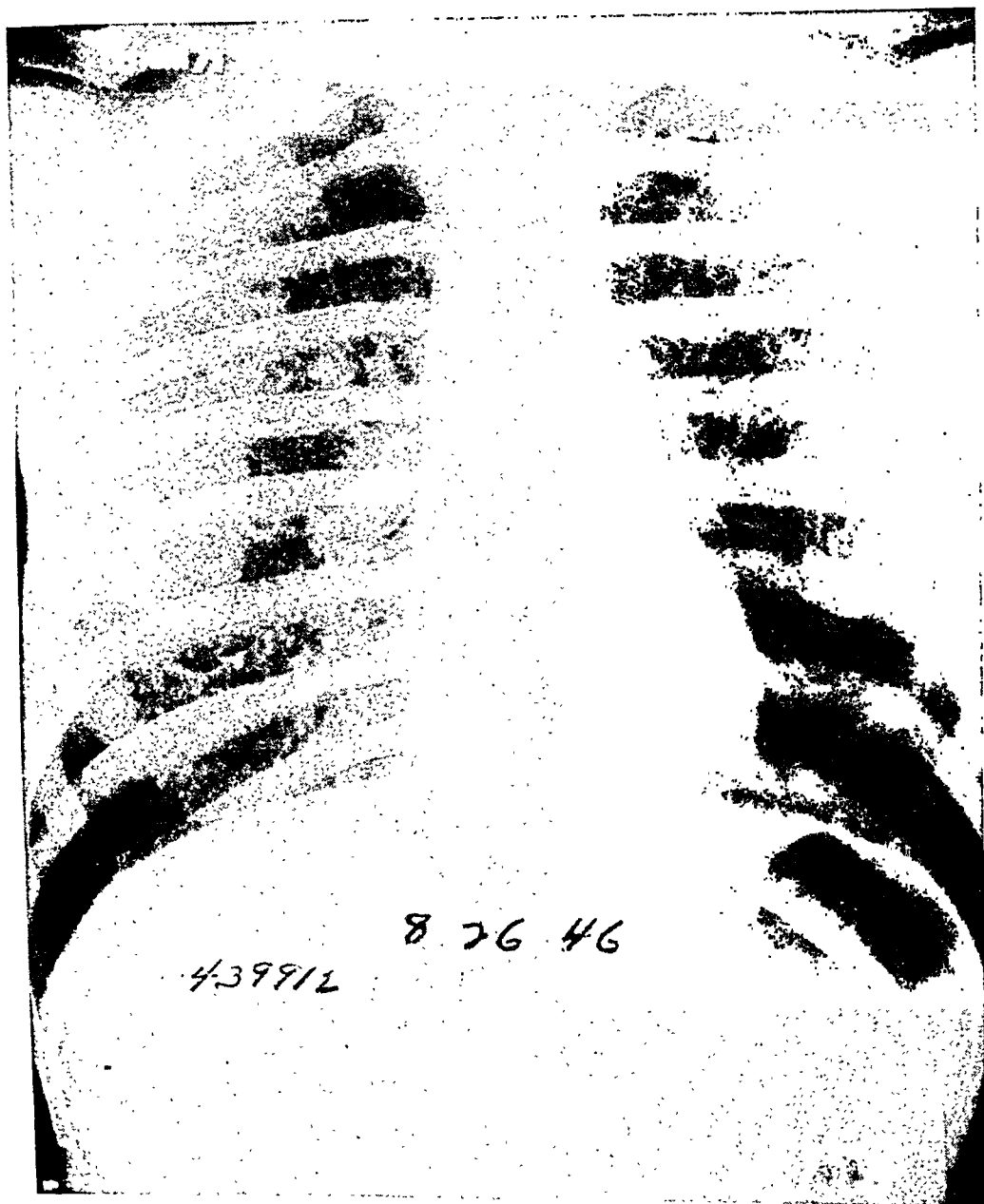


FIG. 4d. Patient C. Co., roentgen-ray of chest one week before death showing reappearance of disseminated miliary infiltrations and widening of supracardiac shadow by lymph nodes which at autopsy were broken down and supplicated.

ciably less rapid. In the two patients who experienced sustained remissions, the total protein values were between 68 and 75 mg. per cent, five months after the cessation of all antimicrobial therapy. It is probable that much of

the pleocytosis and some of the elevation in total protein resulted from the irritating effect of repeated intrathecal instillations of streptomycin and not from the meningitis. In accord with this assumption is the fact that in a case omitted from this series because bacteriologic proof of the diagnosis was not obtained, the amount of protein was within the normal range at the time intrathecal streptomycin was started. During the ensuing 60 days, the quantity of protein rose to 177 mg. per cent, although from all other indications the meningitis was not actively progressing. The patient is a 33 year old man who also attained a satisfactory result five months post-treatment. His illness was characterized by high fever (38 to 40° C.), a

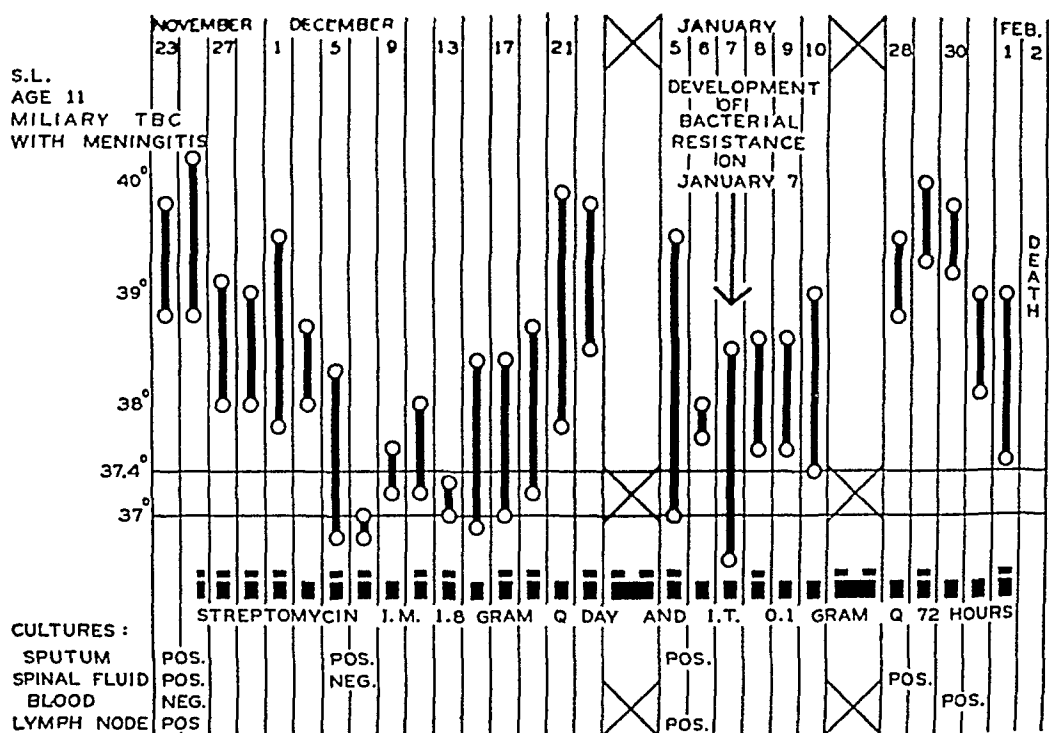


FIG. 5a. Patient S. Le., generalized miliary tuberculosis with relapse under streptomycin treatment. Temperature chart and laboratory data. Note positive blood culture preterminally in relapse.

palpable spleen, four morphologically characteristic choroidal tubercles, clinical evidences of meningitis, and a cerebrospinal fluid which contained 70 lymphocytes per cu. mm. but no abnormal value for sugar or tubercle bacilli on smear or culture.

In summary: Two of nine patients with bacteriologically proved tuberculous meningitis attained remissions which have been maintained for five months after the completion of therapy. In all of the seven unsuccessfully treated cases, the meningitis arose as a complication of an acute hematogenous tuberculosis which was the principal cause of death in all but two instances.

*Generalized Hematogenous Tuberculosis.*

*Acute Miliary Tuberculosis.* Thirteen patients presented the characteristic clinical and roentgenologic findings of acute miliary tuberculosis at the time streptomycin therapy was started. The etiology of the infection was established by culture or guinea pig inoculation in every member of the group.

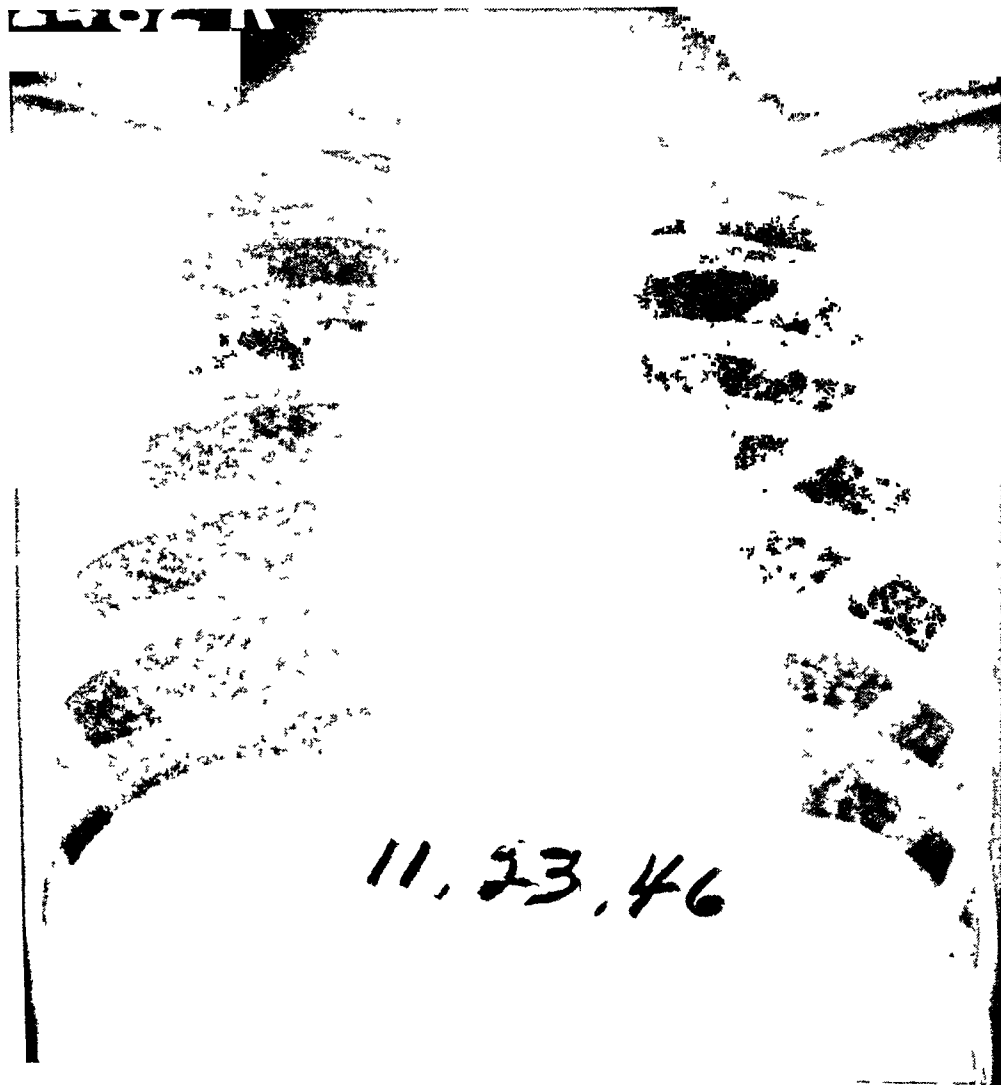


FIG. 5b. Patient S. Le, roentgen-ray of chest before start of treatment.

During the first month of antimicrobial therapy, the course of the infection was essentially the same in all of the 13 patients. There was a prompt reduction in temperature, which frequently attained normal levels within a week of the start of treatment. The defervescence was accompanied by a pronounced change in appearance and symptoms. Individuals who had been critically ill before therapy soon presented the aspect of chronicity or re-



covery. In the sicker patients, mental alertness replaced a state which had resembled that observed in severe typhoid. Enlarged cervical lymph nodes, present in five of the group, receded substantially. In only one instance, however, was there an appreciable reduction in the size of enlarged medi-

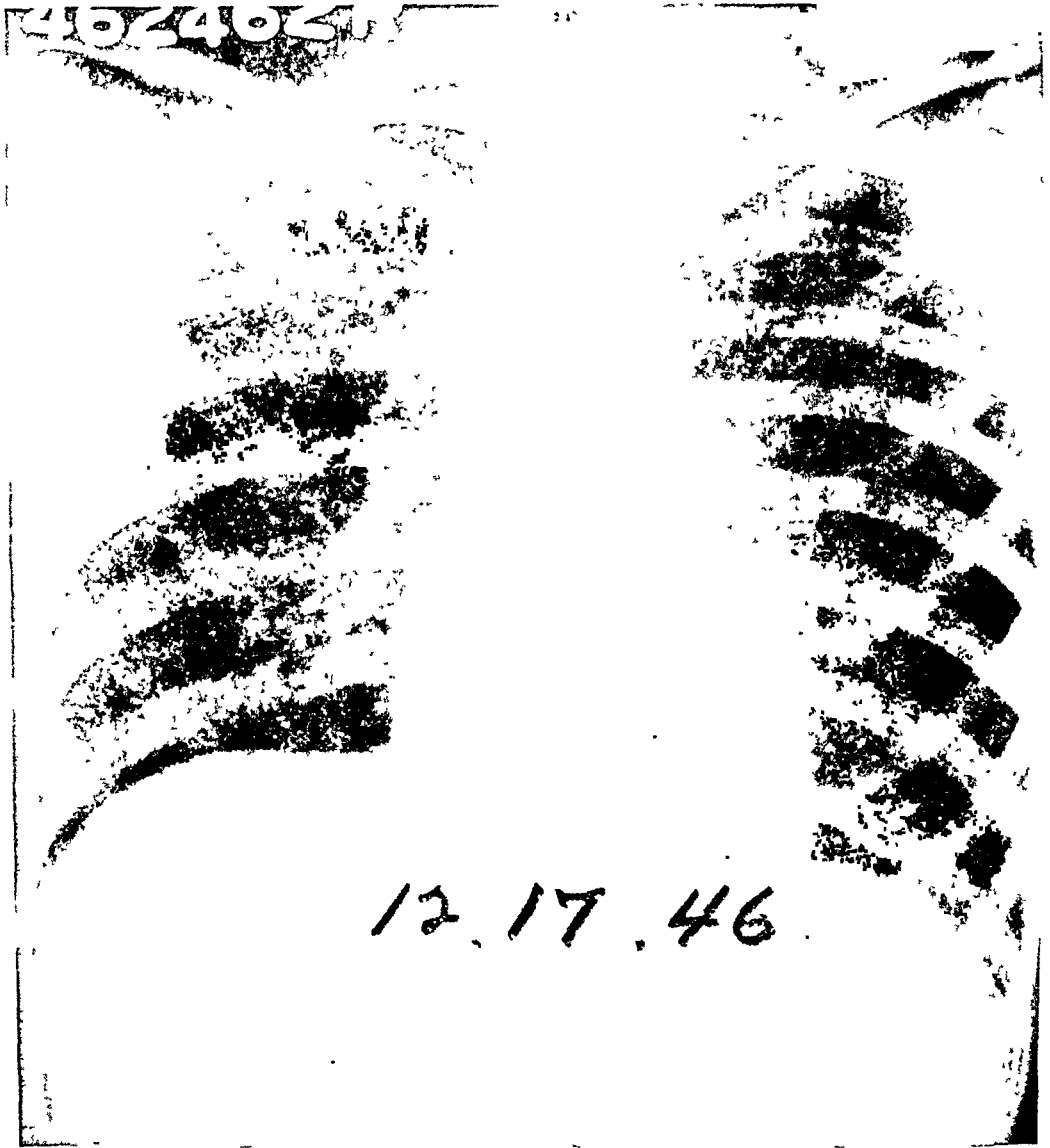


FIG. 5c. Patient S. Le., roentgen-ray four weeks later showing extensive clearing.

astinal nodes. Choroidal tubercles, which had been noted in two patients, regressed considerably during the first month of treatment and eventually disappeared. A weight gain of more than five kilos occurred in three patients, and in the others the weight remained stationary.

The period of rapid clinical improvement was accompanied by a definite reduction in the size of the cardiac silhouette in three patients (figures 6b, 6d

and 6j). Although all of them had been acutely ill at the start of the antimicrobial therapy, they had presented no evidences of pericarditis, or of circulatory failure. This phenomenon remains unexplained.

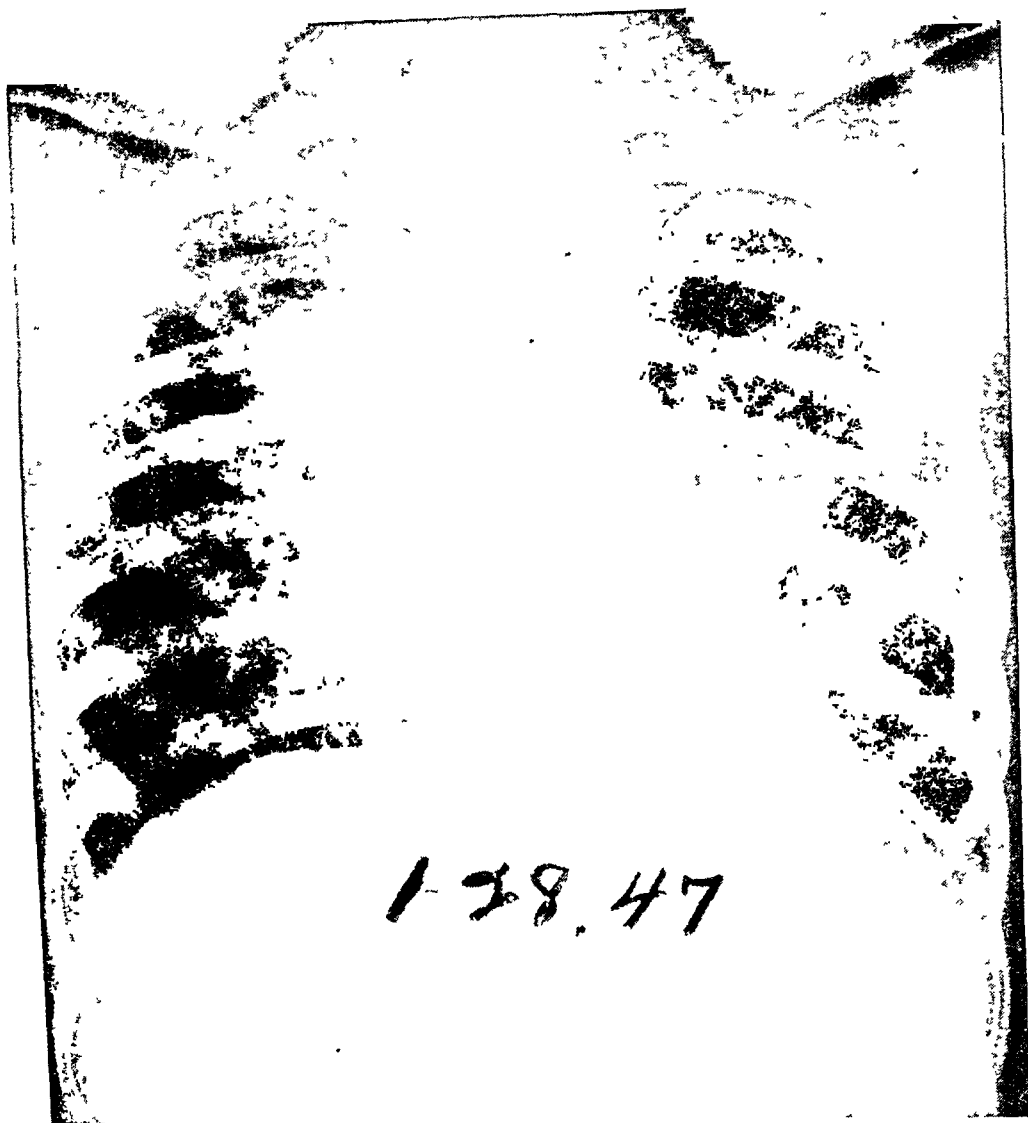


FIG. 5d. Patient S. Le., roentgen-ray five days before death showing relapse.

After the initial improvement, which usually continued throughout the first month of therapy, the course of the individual miliary infections followed one of the four following patterns:

1. Continued improvement with attainment of complete remission \* sustained for at least six months without therapy;

\* Throughout the entire report, the term "complete remission" is used to designate the status of patients who were: asymptomatic; afebrile; discharged no tubercle bacilli; and had absent, stationary, or regressive lesions as determined by roentgenography.

2. Continued improvement with transformation of the acute generalized infection into a chronic disease with residual activity in scattered foci;
3. Continued improvement with sustained remission of the miliary infection followed by fatal meningitis;
4. Partial or complete remission of the signs of infection followed by fatal relapse despite uninterrupted streptomycin therapy.

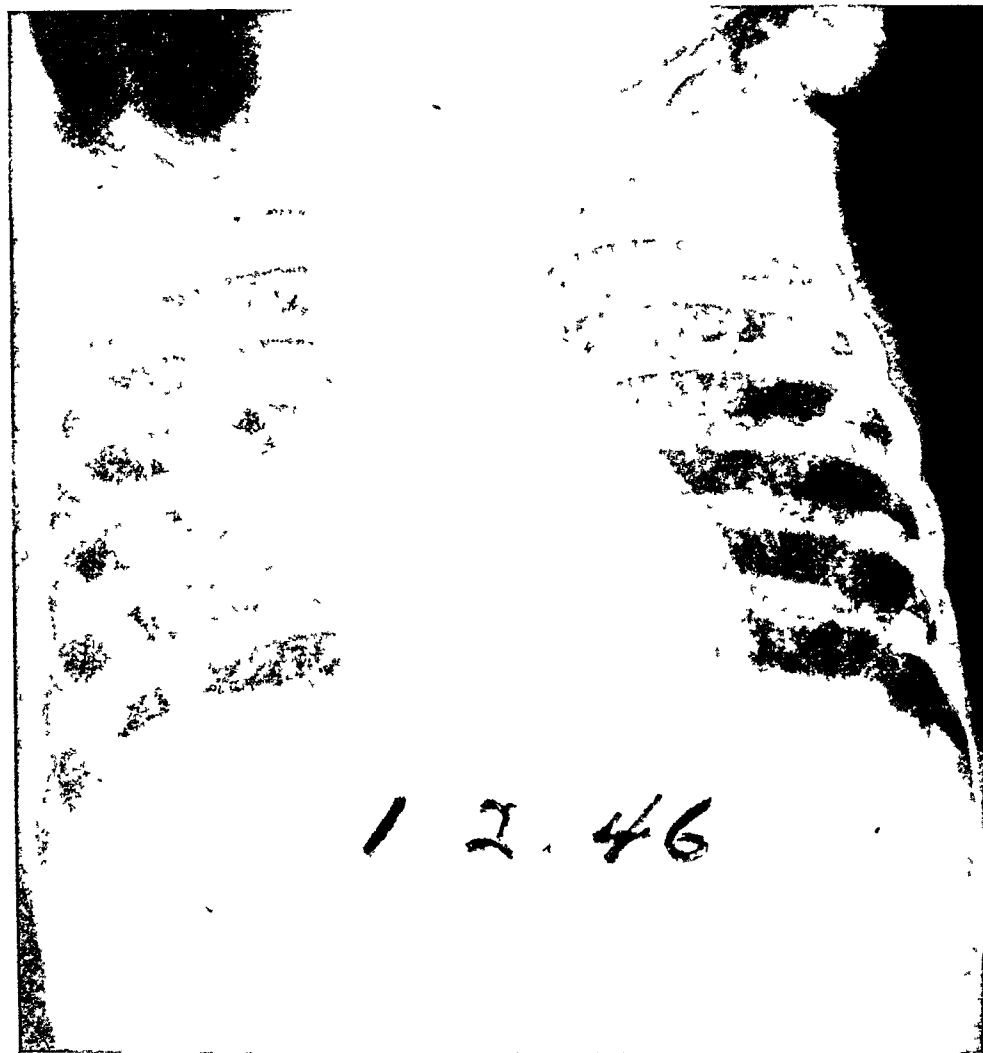


FIG. 6a1.

*Complete Remission.* Only two of the 13 patients developed complete and sustained remissions of the miliary infections (figures 1 and 2). Both are white adults, and in both the tuberculosis can be classified as apparently arrested, according to the N.T.A. standards,<sup>15</sup> six months after the completion of therapy. In one (A. Fo.), the miliary tuberculosis developed in association with involvement of the cervical and mediastinal lymph nodes.

In the other (R. Ph.), the hematogenous dissemination occurred as a complication of pulmonary tuberculosis which had spread after the first stage of a thoracoplasty three and one-half months before the start of antimicrobial therapy. At the time streptomycin was discontinued, neither showed more than slight roentgenologic evidences of miliary tuberculosis, but the mediastinal lymphadenopathy was still present in one, and the residuum of the



FIG. 6a2.

pulmonary tuberculosis persisted in the other. It is of interest that in each of them there was a virtually complete clearing of these residual processes in the six months subsequent to the completion of the antimicrobial therapy.

*Transformation into Chronic Infection with Residual Activity in Scattered Foci.* The apparent transformation of the acute miliary tuberculosis into a chronic infection was observed in only one patient, an extremely cachectic and desperately ill woman of 22. After an initial period of improvement manifested by abrupt defervescence and disappearance of choroidal

tubercles, she developed an intermittent fever ( $37^{\circ}$  to  $38.5^{\circ}$  C.) with the appearance of chronic illness. Repeated cerebrospinal fluid examinations failed to reveal meningitis, but at no time during the first three months of therapy was there clear and definite evidence that she would recover. She improved steadily and gradually during the last month of treatment and in the immediate post-treatment period her improvement was impressive. Her

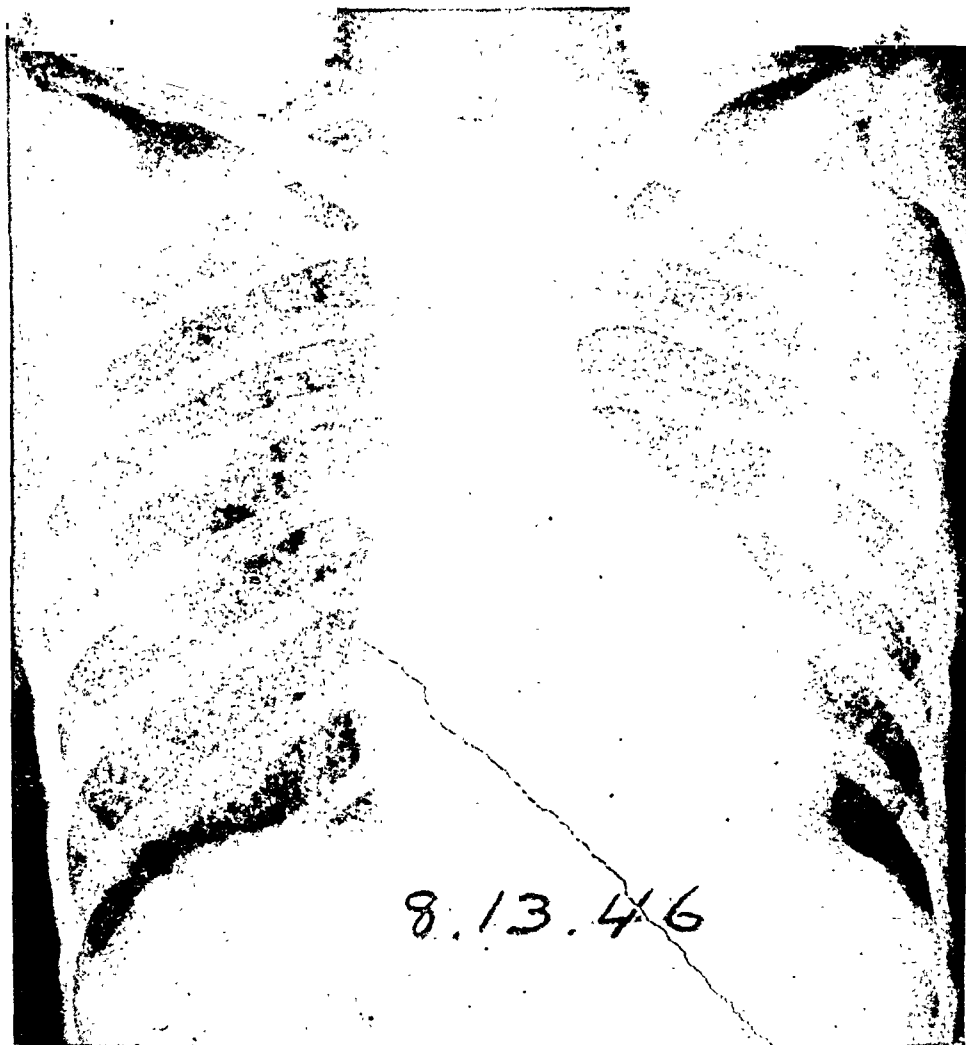


FIG. 6b1.

temperature was maintained in the normal range, and she gained 8.5 kilograms in weight. Ten weeks after the cessation of therapy, she developed signs of pleuritic and pericardial involvement accompanied by a return of fever. Although the possibility of a second hematogenous dissemination cannot be excluded, clinical or roentgenologic evidence was lacking. Streptomycin therapy was reinstituted for a six-week period and was accompanied by prompt defervescence and disappearance of symptoms. During

the two and one-half months since completion of the second course of treatment (10 months after therapy was first started), the patient has remained asymptomatic.

In consideration of the unusual course of this infection, it may be relevant that, in the 10 month period since the start of antimicrobial therapy, no

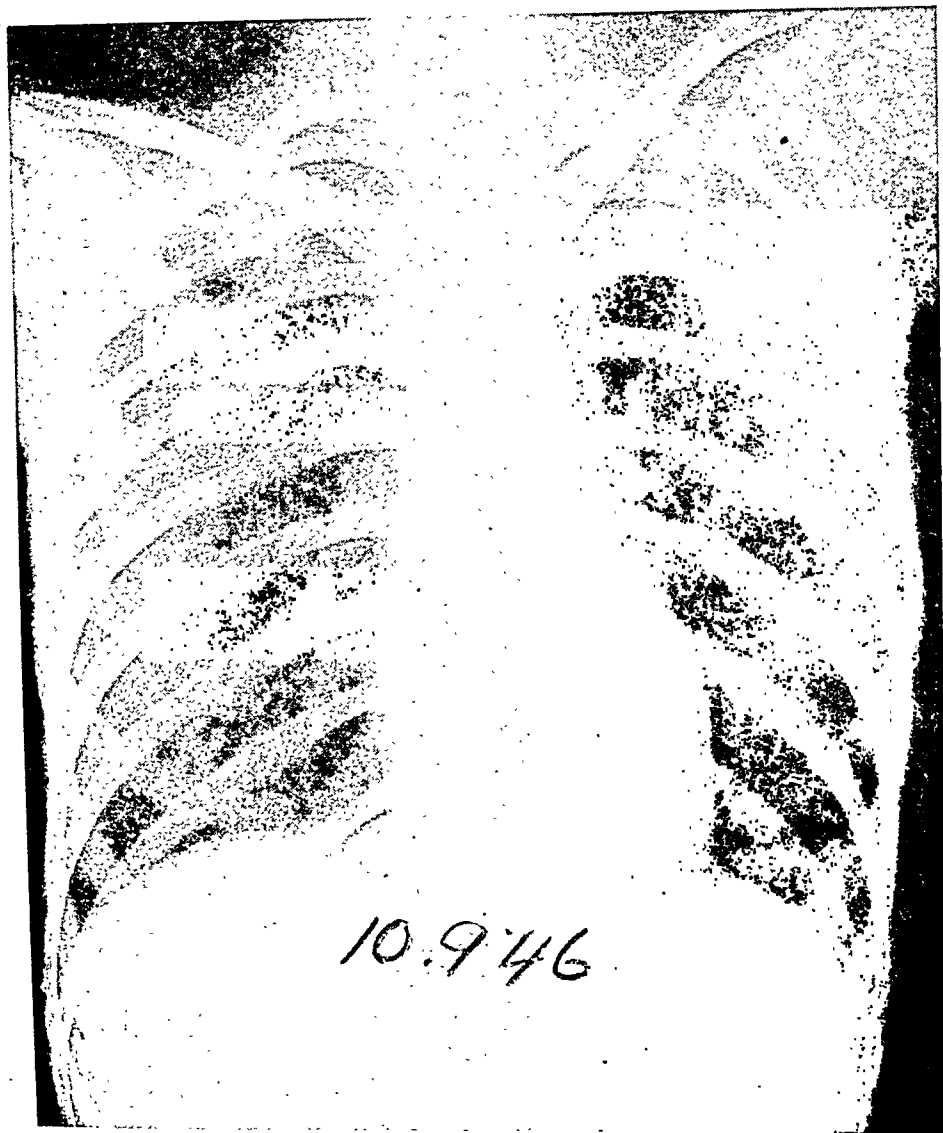


FIG. 6b2.

change in the scattered densities in the roentgenogram has been noted (figure 3). Moreover, each of these densities are two to three times larger than the shadows usually cast by the lesions of miliary tuberculosis. It is established, however, that these large (2 to 5 mm.) densities represented an early process, for they appeared under observation during the four weeks immediately preceding the initial course of streptomycin therapy. This patient's miliary

infection is the only one in the entire series in which marked roentgenologic clearing failed to occur.

*Complete Remission of Miliary Infection with Death from Meningitis.* Complete recovery from the miliary infection with eventual death from meningitis occurred in only one patient, the 18-month infant whose case has been previously described. The completeness of the recovery from the hema-

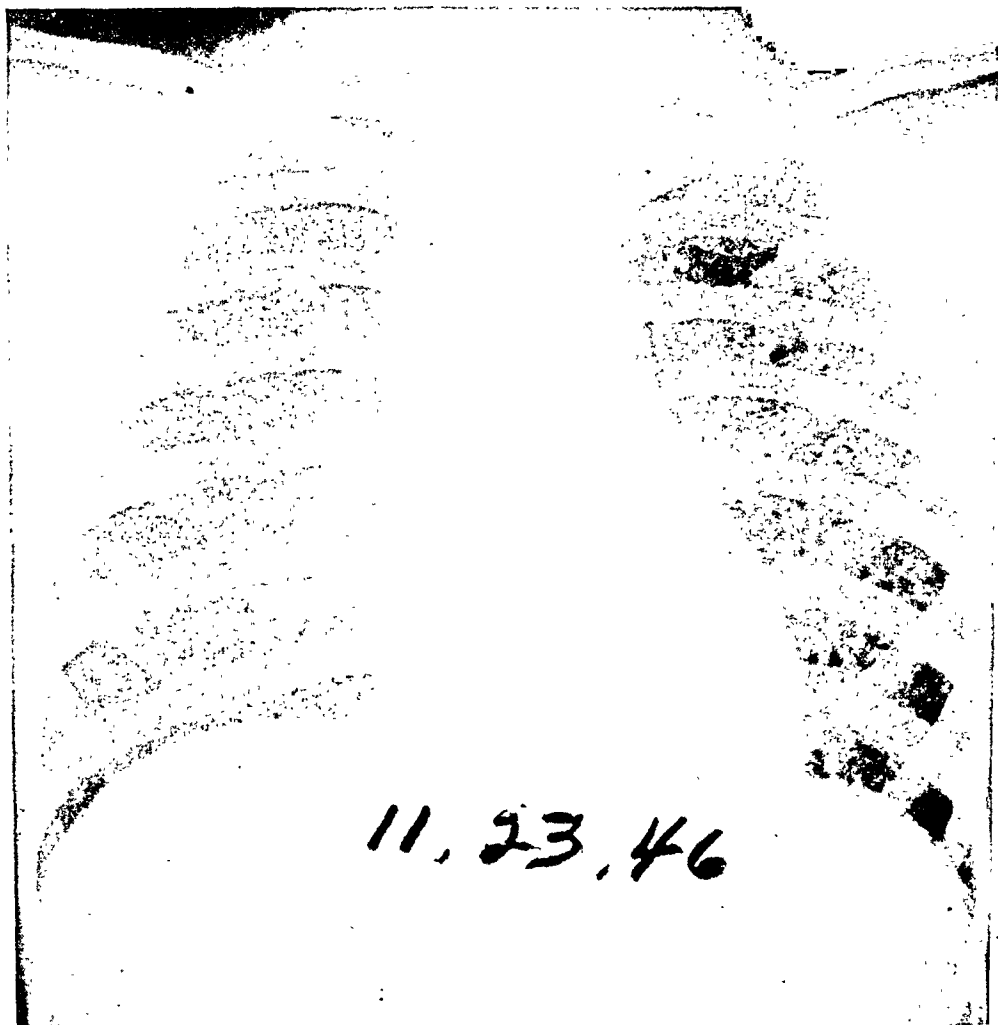


FIG. 6c1.

togenous disease was substantiated by the histopathologic findings obtained 11 months after the start of streptomycin therapy. These observations are presented in detail below.

*Diphasic Course.* The course of infection which was most frequently observed in the entire series was a diphasic type of miliary tuberculosis which eventually resulted in death. The diphasic response occurred in five patients. In all but one instance, the fatal relapse developed while the patient was

receiving streptomycin. The exception was a patient whose fatal relapse appeared 17 days after the cessation of a second course of therapy, and was completely unaffected by the reinstitution of streptomycin.

The first phase of the diphasic course consisted of the period of rapid improvement. During the first month of antimicrobial therapy, there was

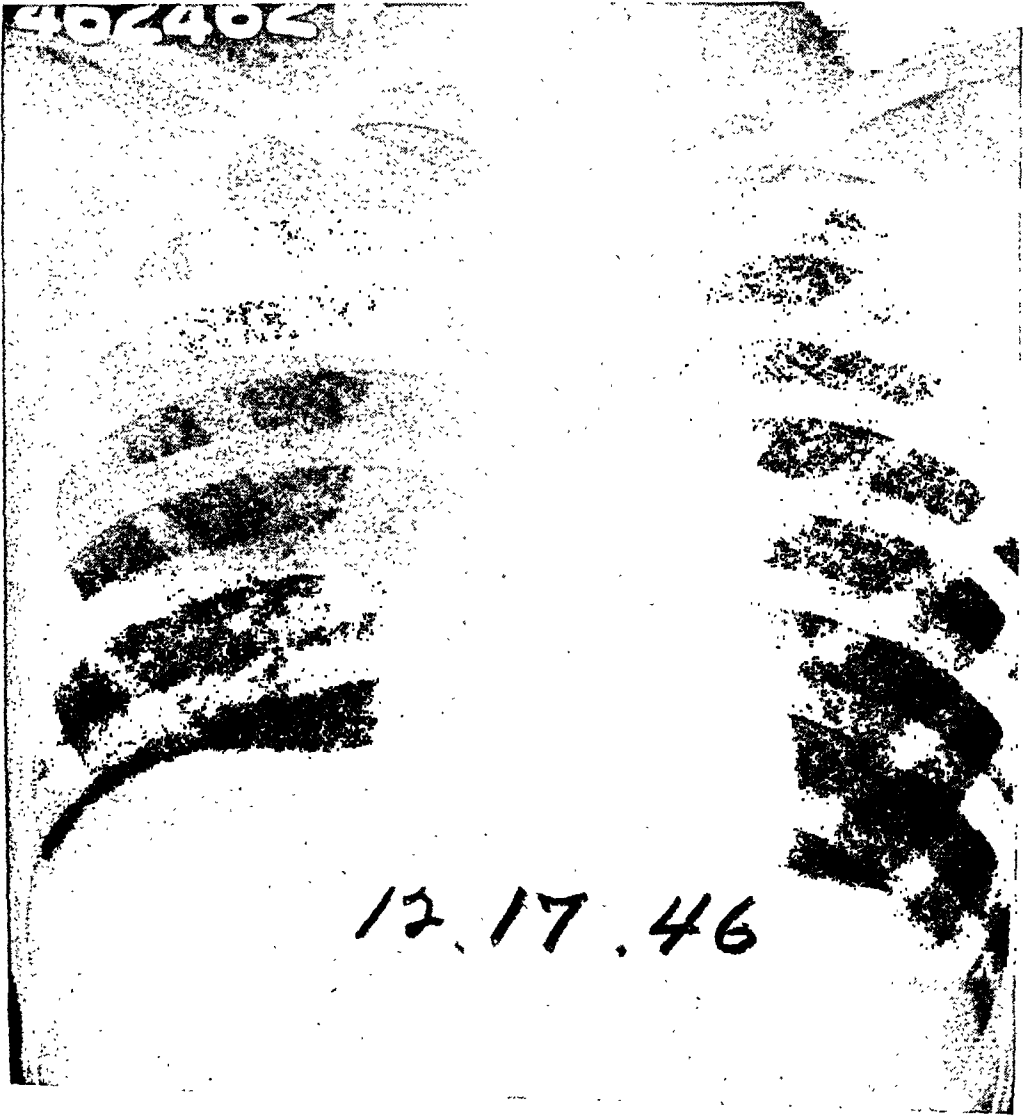


FIG. 6c2.

complete or virtually complete regression of all of the presenting clinical evidences of tuberculous infection. The principal clinical manifestations so affected were: enlargement of the superficial lymph nodes (five patients); pharyngeal and laryngeal lesions (two patients); choroidal tubercles (two patients). The cerebrospinal fluid findings of tuberculous meningitis were present at the start of therapy in two individuals and appeared between the



thirty-fifth and ninety-sixth days of treatment in three others. In these patients, however, the meningitis was never a significant factor in the total illness and, in some instances, produced no clinical manifestations. In all five patients, the clinical improvement was accompanied or followed by an extensive clearing of the miliary densities demonstrable on the roentgenogram.

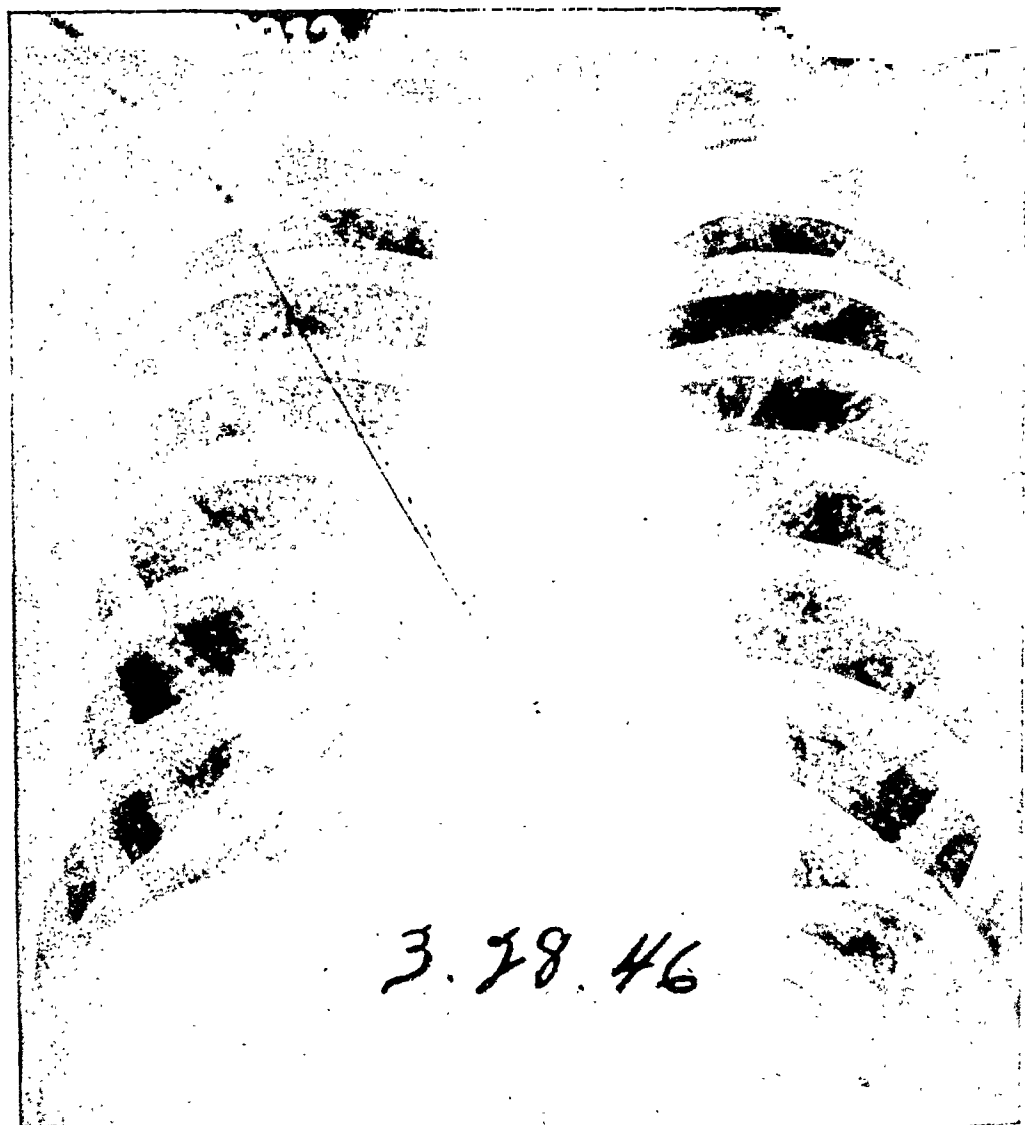


FIG. 6d1.

The extent of both the clinical and the roentgenologic changes varied among the individual patients, but in every member of the group the improvement was marked. Although the majority of the patients did not appear to be completely well, they usually presented no more evidence of disease than a continued low-grade fever. In one patient a complete re-

mission was attained and continued for three and one-half months after the cessation of therapy.

The most extreme example of the diphasic phenomenon, however, was observed in a 21 year old white man (figure 4). After two months of

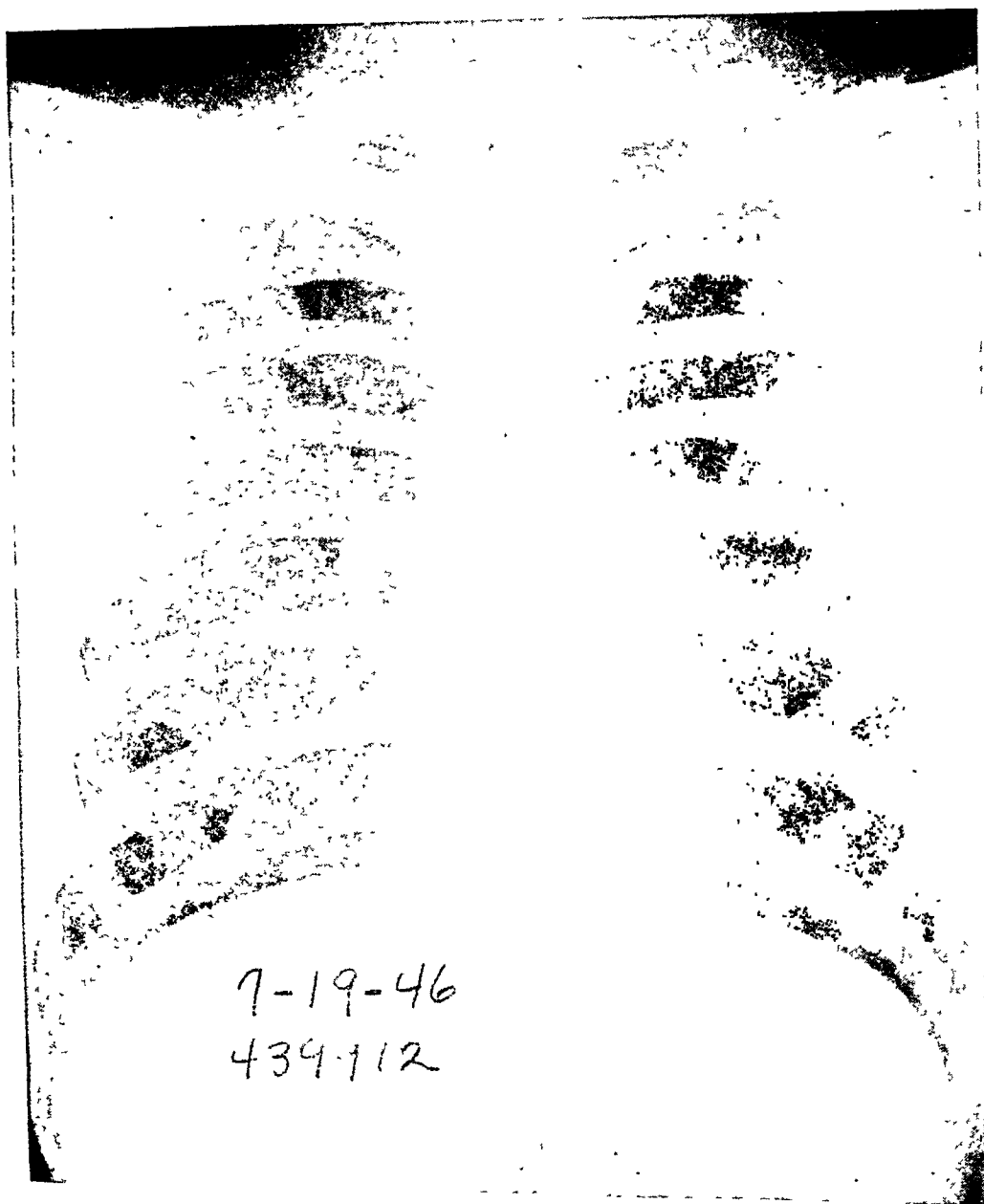


FIG. 6d2.

streptomycin therapy, this patient presented no clinical, roentgenologic, or bacteriologic signs of miliary tuberculosis, although all three types of evidence had been present prior to treatment. The complete remission was maintained for approximately five weeks until the beginning of the fo

of the use of streptomycin. At this time, although therapy was not interrupted, the cervical lymph nodes enlarged and discharged bacilli, fever returned, and the miliary densities were again visible upon the roentgenogram. The infection resumed the rapidly progressive character which it had displayed before treatment, and the patient died at the end of the fifth month of

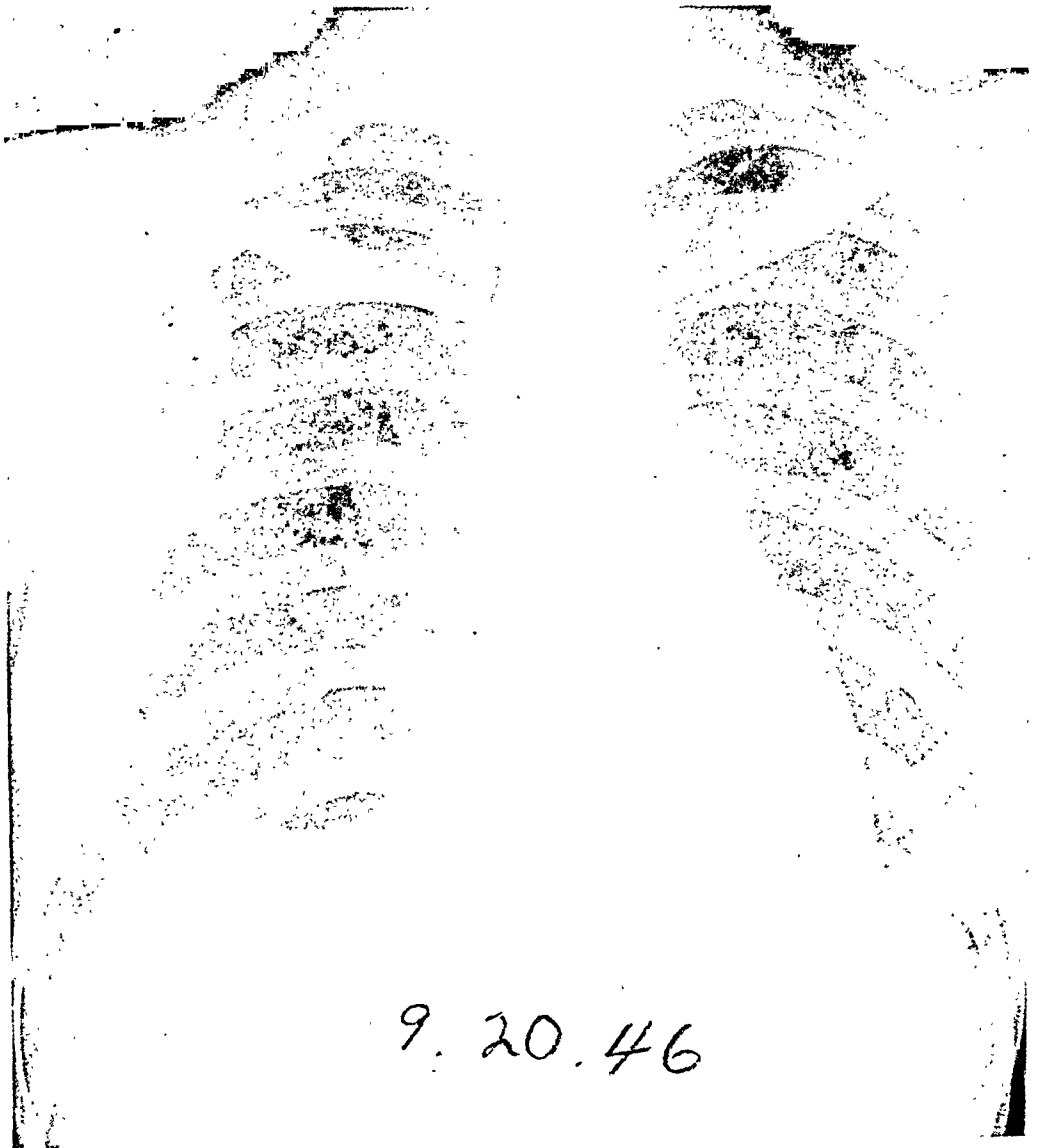


FIG. 6c1.

streptomycin therapy. During the last 10 days of life he was given nine grams of streptomycin daily with no apparent effect upon any manifestation of the infection.

In the other three patients in whom relapse appeared while under therapy, the onset of the phenomenon appeared on the twentieth, fifty-second and

sixty-sixth days of therapy respectively. The onset was heralded by a return or an increase in fever, and by the reappearance of clinical signs of tuberculosis such as enlarged lymph nodes or ulcerative pharyngeal lesions which, in some instances, had been present before the initial generalized hematogenous infection. Approximately two to three weeks after the first

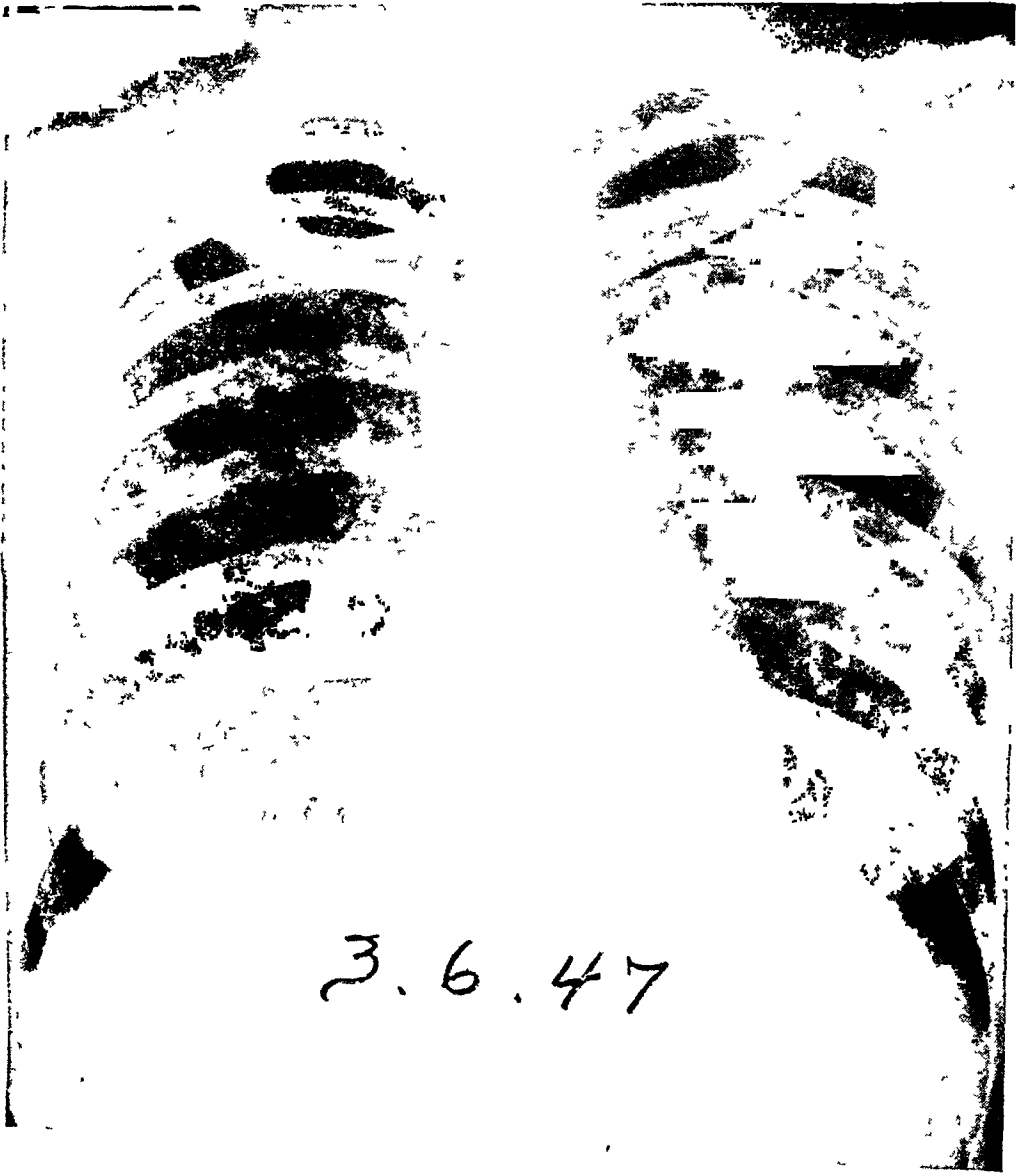


FIG 6c2

sign of relapse, the miliary densities reappeared on the roentgenogram. All signs of infection steadily progressed despite the antimicrobial therapy, and, in all four individuals, death occurred between the thirty-eight<sup>th</sup> and fiftieth days after the onset of relapse.

The demonstration of a bacteremia in one patient (figure 5) and the

appearance of choroidal tubercles for the first time in another is evidence that in some instances a fresh hematogenous dissemination occurred in association with the relapse.

Two episodes of relapsing miliary tuberculosis occurred in the fifth member of the group. The first relapse developed three and one-half months

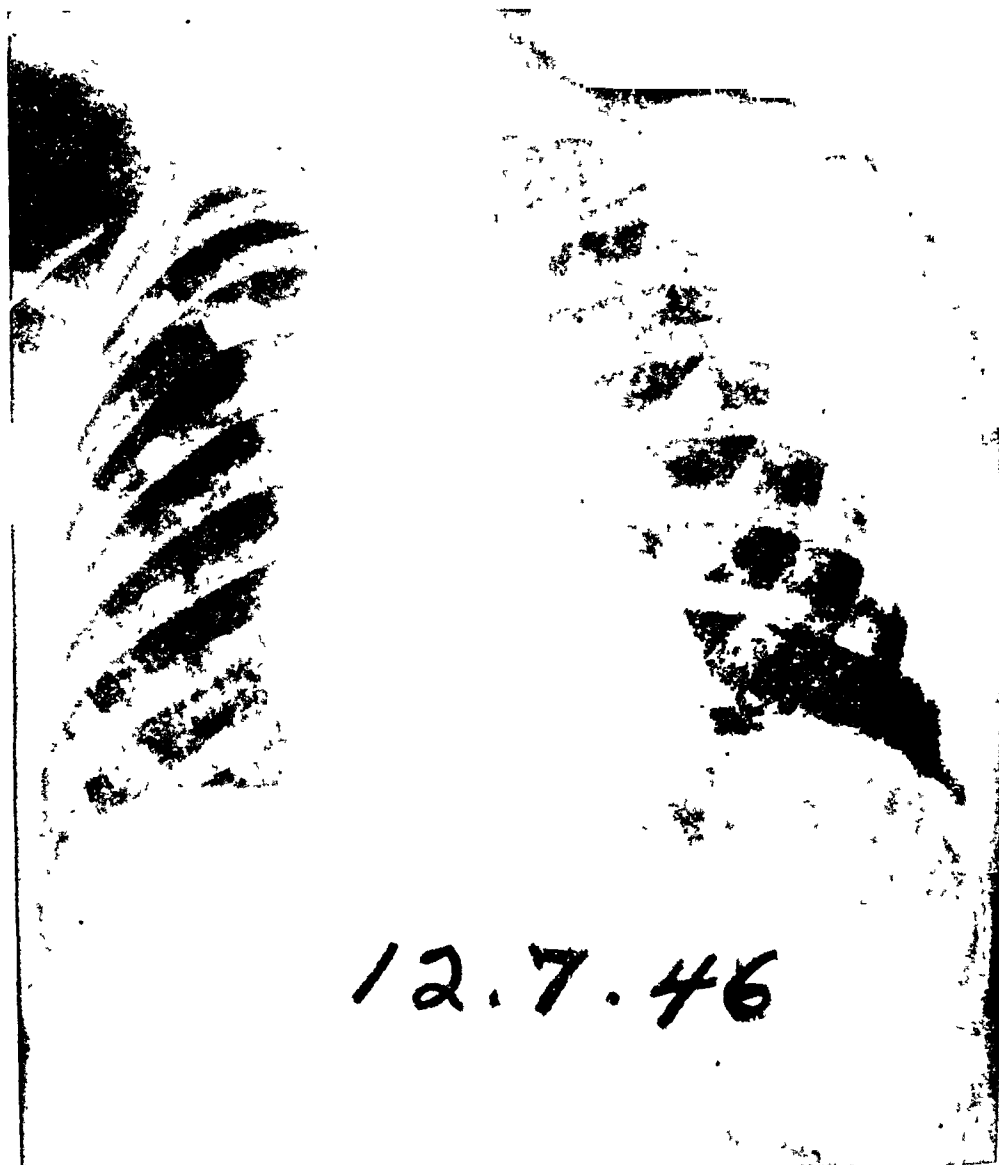


FIG. 6f1.

after a 60 day course of therapy, and appeared to respond to the readministration of streptomycin. The second appeared 17 days after the cessation of a 90 day course of treatment, and was completely uninfluenced by the further administration of antimicrobial therapy. Death occurred within five days of the start of the third course of streptomycin (i.e., 119 days after the start of the 90 day course of therapy). It is probable that this relapsing in-

fection proceeded by the same mechanism as was operative in the other four cases.

Tubercle bacilli isolated from four of the five patients at the onset of relapse under therapy were highly resistant to streptomycin in vitro. Organisms could not be cultured from the other individual at the exact onset of

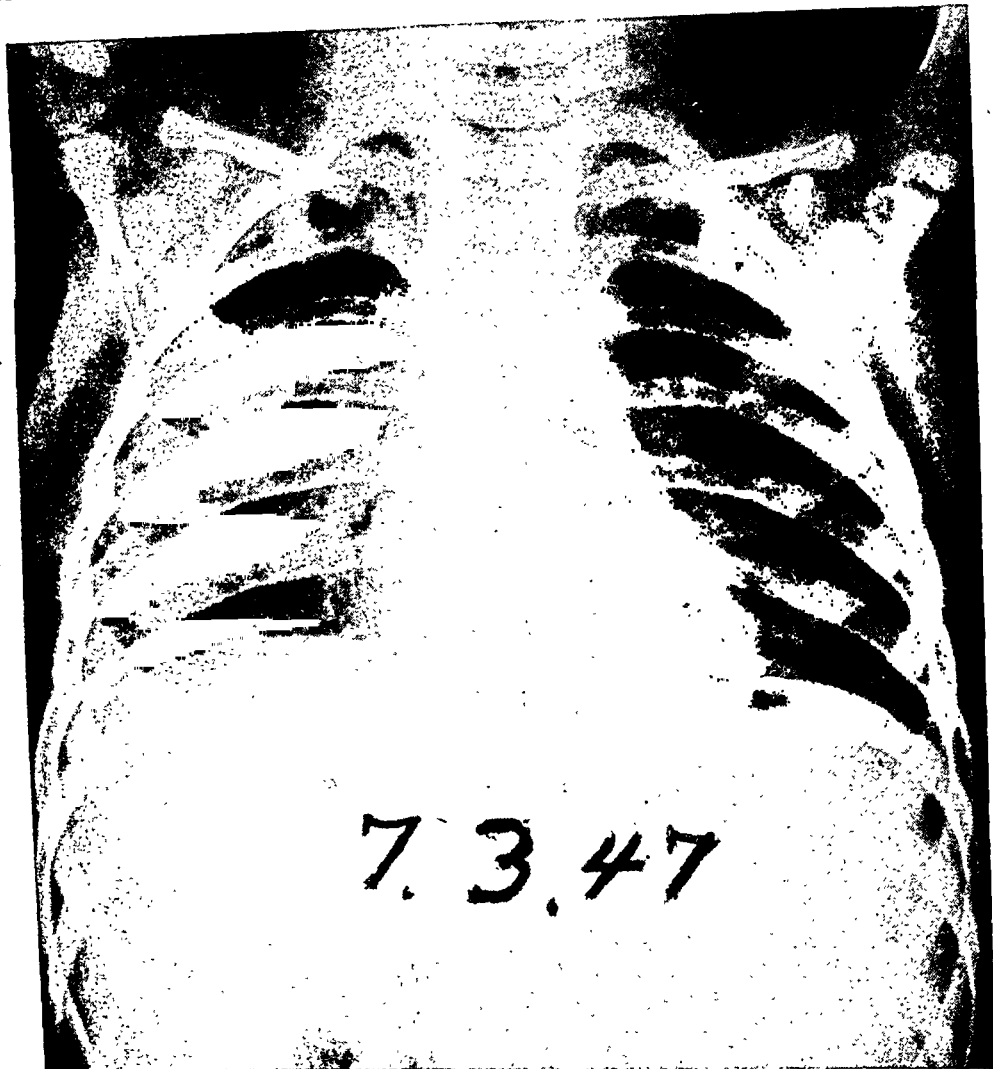


FIG. 6f2

relapse. Postmortem cultures of the lungs of this patient yielded tubercle bacilli which grow so poorly on artificial media that satisfactory streptomycin sensitivity determinations have not been possible.

*Roentgenologic Changes in Acute Miliary Tuberculosis.* The roentgenologic changes which were observed in 11 patients with acute miliary tuberculosis are presented in figure 6.\* In a few instances, a considerable

\* Figure 6 consists of 11 pairs of films (6a1-6a2, 6b1-6b2, etc.). The first film in each pair shows the extent of the miliary process prior to therapy and the second the extent of clearing. The second film is not necessarily the earliest film taken that showed extensive clearing. Refer to pages 788 to 813.

amount of clearing occurred during the first month of therapy. In general, however, there was little or no change until the second month of treatment, which represented the period during which the maximum degree of change occurred in the group as a whole. Regardless of outcome, a complete disappearance of the densities of the miliary tuberculosis occurred in eight in-

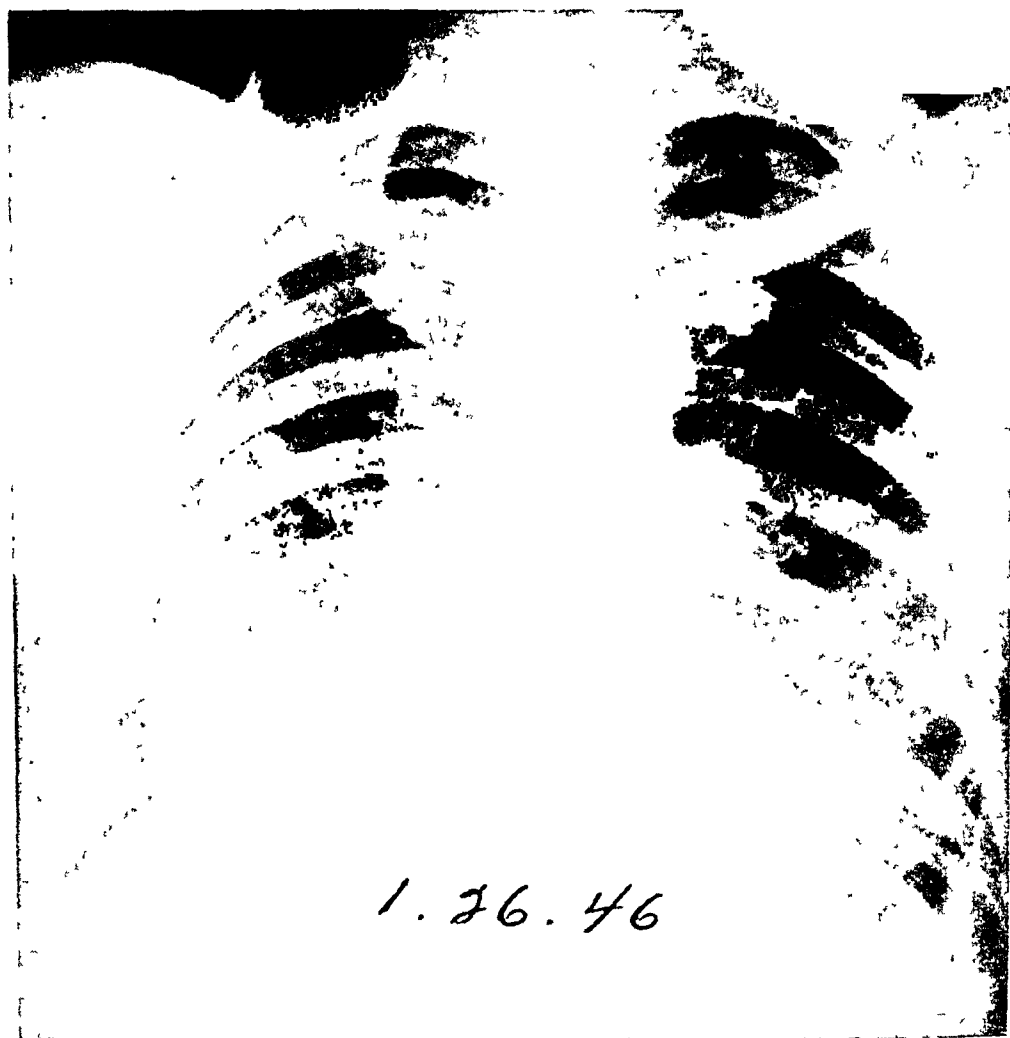


FIG. 691.

dividuals at some time during treatment. In the course of relapse, densities were observed to reappear in two to four weeks after the most recent previous film. As noted previously, in one patient there was no demonstrable change in the densities throughout a 10 month period of observation.

*Other Hematogenous Forms (Non-Miliary).* Two patients presented the clinical picture of an acute hematogenous infection, but never developed the characteristic roentgenologic findings of acute miliary tuberculosis. One had tuberculous pericardial effusion associated with lymphadenitis and bac-

teremia; and the other had disseminated lesions of bone associated with long-continued high fever.

In both, the institution of streptomycin therapy was followed by a reduction in fever and a marked improvement in general appearance and symptoms. In the patient with the widespread lesions of bone, all but one of 11 ex-

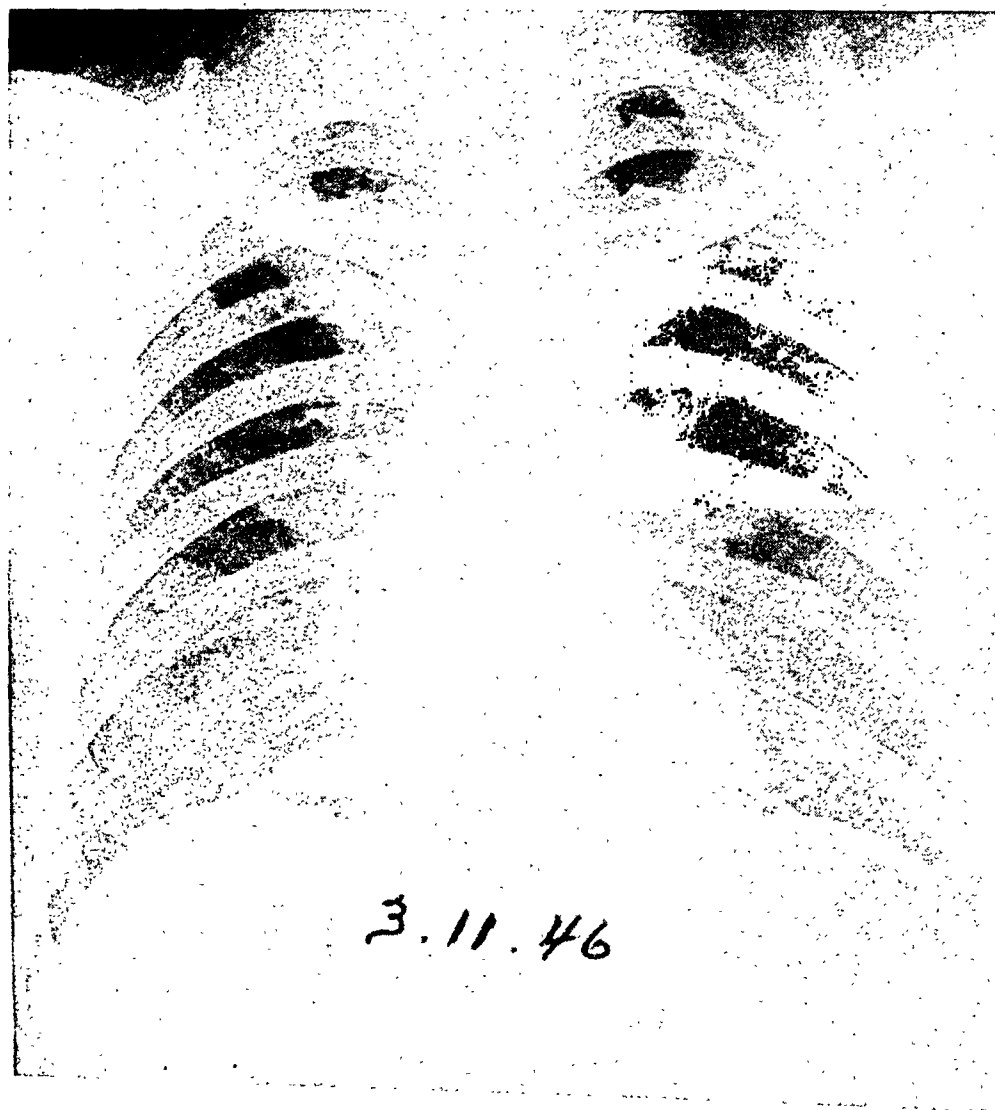


FIG. 6g2. Same patient as figure 6g1, showing extensive clearing.

ternally draining sinuses healed completely within the first eight weeks of antimicrobial therapy and the remaining one healed thereafter. The cutaneous fistulae have remained closed during the eleventh-month period since the start of streptomycin therapy. There has been no change, however, in the roentgenologic appearance of the various scattered lesions of the bones. It is of interest that at no time did this patient show any roentgenologic or bacteriologic evidence of tuberculosis of the lungs.



The patient (figure 7) with tuberculous pericarditis is a 19 year old colored girl who developed an acute tuberculous pericarditis with effusion during the third month of a rapidly progressing tuberculosis of lymph nodes. Tubercle bacilli were cultured from pericardial fluid, lymph node, and on one occasion from the circulating blood, prior to the institution of streptomycin

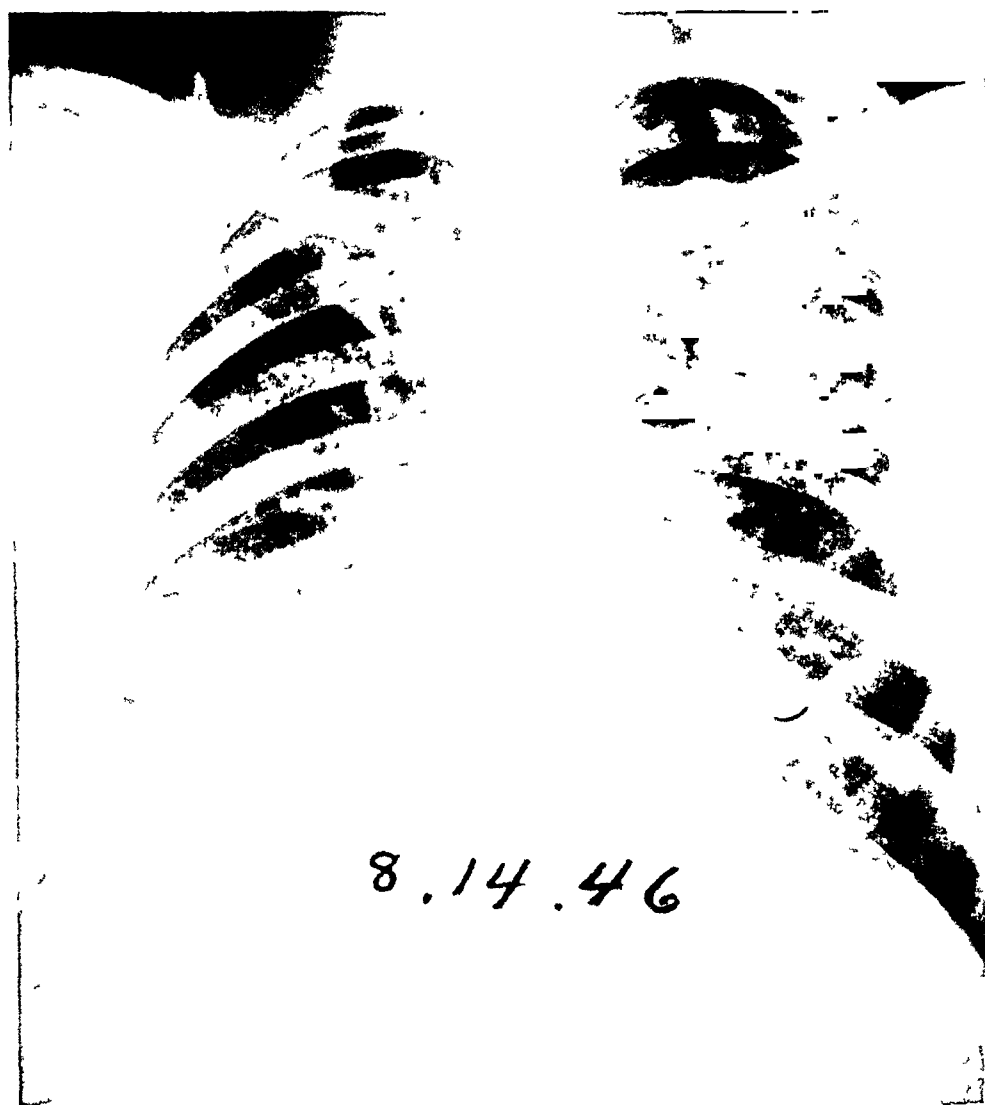


FIG. 6g3. Equally striking change when patient was retreated after relapse.

therapy. Immediately before treatment, the patient was acutely ill and unable to lie flat in bed, although frank signs of cardiac compression were not present. Pericardesis was performed in the week preceding the start of antimicrobial therapy and 100 c.c. of fluid were removed on that occasion. Subsequent aspirations, after the start of treatment, were performed not because of tamponade but in order to obtain specimens for streptomycin assay.

During the first five days after the start of antimicrobial therapy, there was a prompt fall in temperature which was associated with a complete disappearance of symptoms. The clinical improvement was maintained and it became impossible to isolate tubercle bacilli by culture. There was a gradual reduction in the size of the cardiac shadow during the four months

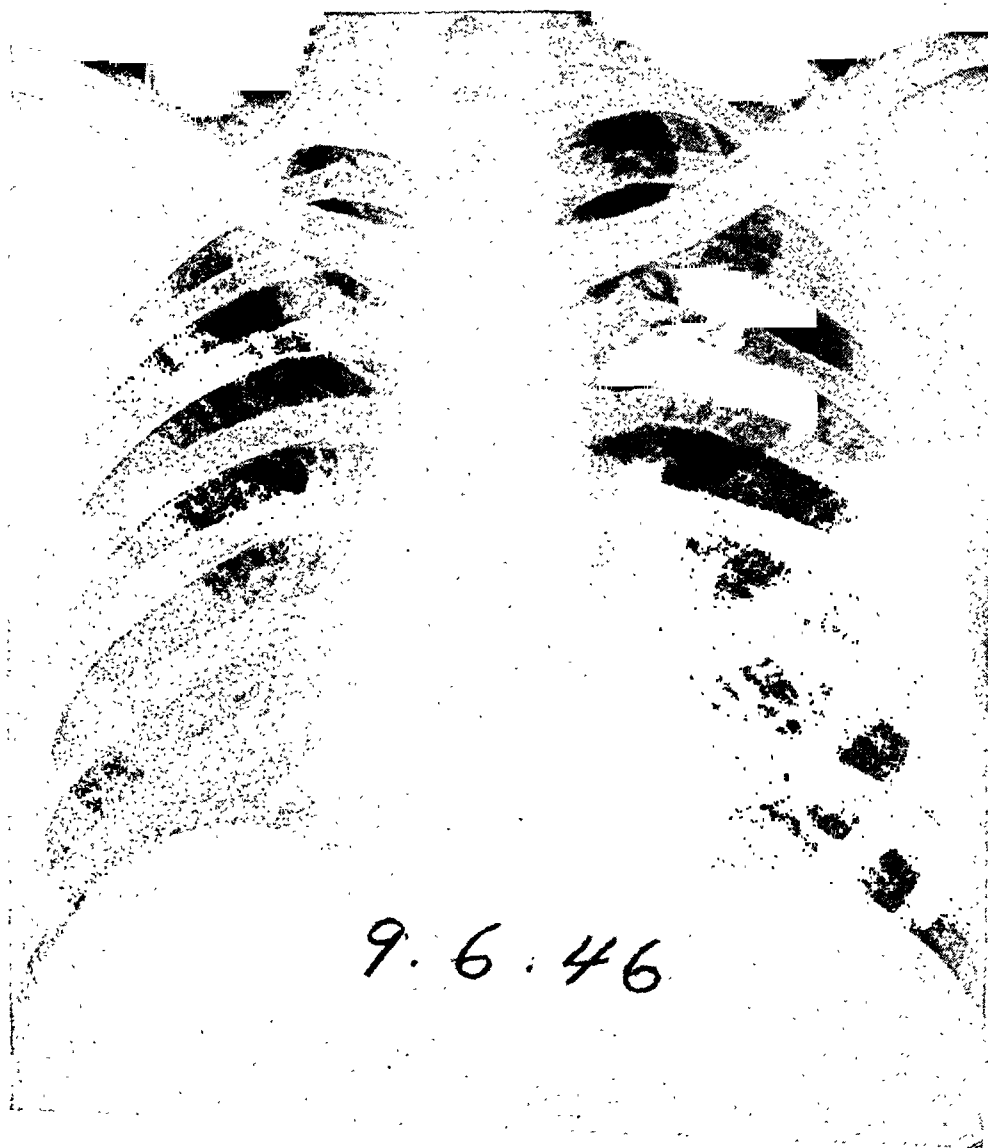


FIG. 6g4. Same patient as preceding figure.

period of therapy. In the ensuing months, still further reduction occurred but an enlargement of approximately 15 per cent persisted. The shrinkage of the cardiac shadow was not followed by any signs of constrictive pericarditis.

Eleven months after the completion of therapy the patient is afebrile,

asymptomatic, has negative cultures, and is leading an ambulatory existence at home.

*Streptomycin Sensitivity.* Of the entire group of 17 patients with bacteriologically proved generalized hematogenous or meningeal infections, it was possible to determine the streptomycin sensitivity of the pre-treatment

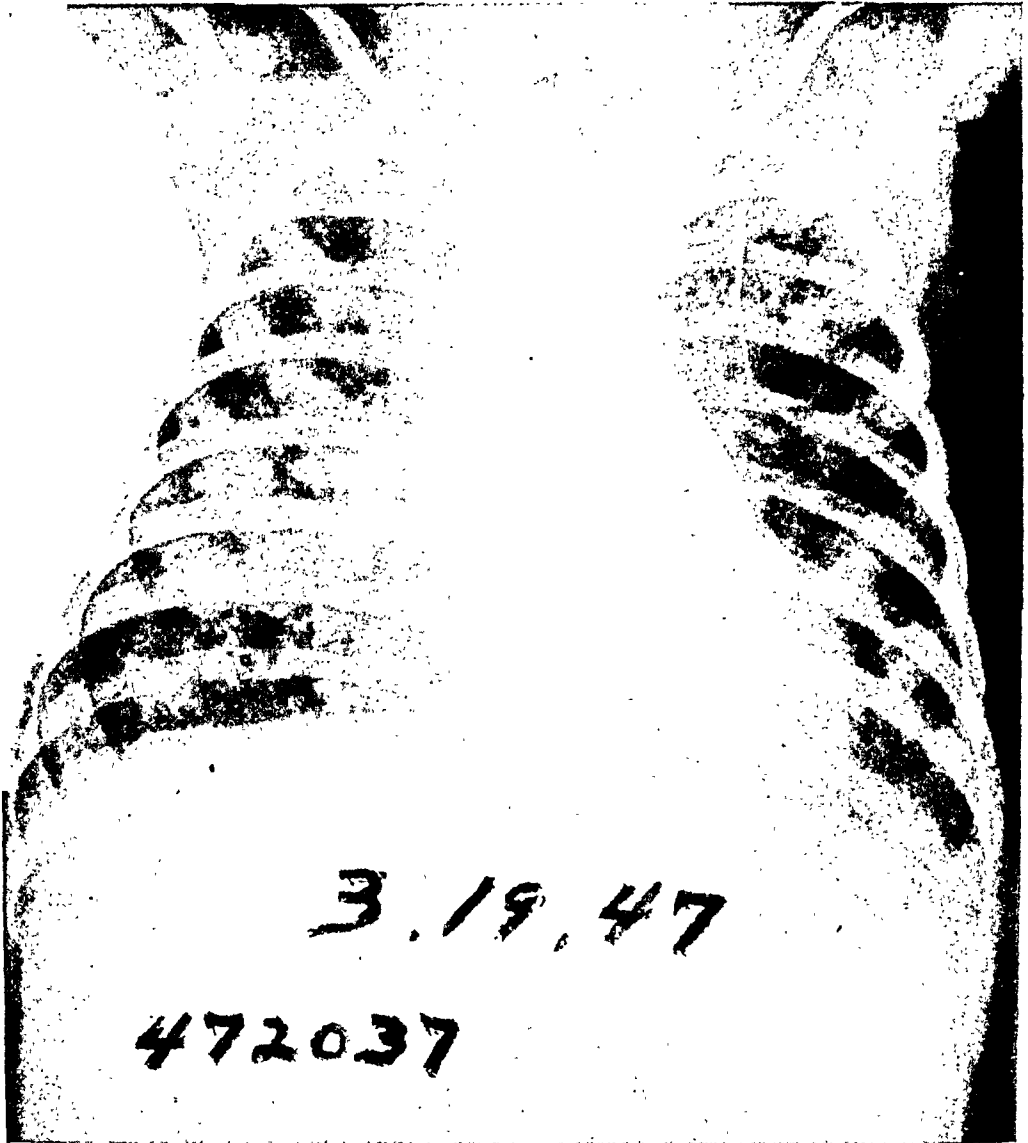


FIG. 6h1.

strains of tubercle bacilli in all but two. The results are presented in tables 1 and 3. Organisms cultured from the cerebrospinal fluid are considered separately from the bacilli isolated from sputum, gastric washings, lymph nodes, and the circulating blood. The reason for this distinction lies in the fact that, with the intrathecal administration of streptomycin, the organisms

within the central nervous system have a potential exposure to streptomycin concentrations as high as 1500 to 2500 micrograms per c.c. of cerebrospinal fluid. In contrast, after intramuscular administration of 3.0 grams daily in divided doses, the organisms resident in tissues other than the central nervous system are seldom exposed to streptomycin concentrations greater than 50 micrograms per c.c. of plasma or extracellular fluid.

TABLE II  
In Vitro Streptomycin Sensitivity of Cultures from Generalized Hematogenous Infections Exclusive of Meningitis

Patient	Source of Culture	Pre Treatment	Months After Start of Intramuscular Therapy								Remarks
			1	2	3	4	5	6	7	8	
A FO	Lymph node	S									Subsequent cultures of lymph node, gastric washing, blood and urine were all negative
C ST	Blood	S									
	Pericardial fluid	S	OO								No pericardial fluid obtained after second week
J WA	Gastric washing	S			O	O	O				Subsequent cultures of gastric washings negative to date
G MU	Cutaneous sinus	S		O	O	O					No material for culture available after 3 months
A KE	Sputum	S		S*							
R PH	Sputum	S	O	OO	S	O	O O	O OO	O	O	
G TE	Sputum	S		R R	R						Died 4th month
S LE	Abscess	S		R	R*						
	Blood	O				R					
	Urine	S		R							
E DE	Sputum	S			R	R*					
C CO	Lymph node	S					R	R*			
	Gastric washing	S	O	O		I					

O—Negative culture  
S—Sensitivity < 2 mcg./c.c.  
I—Intermediate sensitivity  
R—Resistant > 500 mcg./c.c.  
\*—Postmortem culture

In table 2 may be seen the streptomycin sensitivities of bacilli obtained from the systemic infection of 10 patients with generalized hematogenous tuberculosis (8 with miliary infections). All of the strains tested before treatment were completely inhibited in vitro by streptomycin concentrations of less than two micrograms per c.c. of medium.

In six cases, organisms could not be isolated after the end of the second month of antimicrobial therapy, and all organisms obtained before that time were streptomycin-sensitive in vitro. (One patient died after only 40 days of treatment and organisms obtained at death were still sensitive to strepto-

mycin.) In the only other fatality (post-meningeal hydrocephalus), tubercle bacilli could not be cultured from the tissues post mortem.

In four patients from whom organisms were obtained subsequent to the sixtieth day of treatment, the bacilli were not inhibited in vitro by concentrations of 500 micrograms of streptomycin per c.c. of medium.\* The results of the tests of the organisms obtained at post mortem from the fifth patient were equivocal. All of this group of five died as a direct consequence of the tuberculous infection. The shortest period required for the appearance of a resistant strain was 34 days.

TABLE III  
In Vitro Streptomycin Sensitivity of Cultures from Cerebrospinal Fluid

Patient	Pre Treatment	Months After Start of Intramuscular Therapy								Remarks
		1	2	3	4	5	6	7	8	
H RA	S	OOOO	OOO	OO						
C SN	S	S000	0000	0000	0000	O		O		
S LE	S	O O	O O							Died 68 days after treatment started
R HE				SO O	OO	O	O			
A KE	S	S OO	OI*							
E DE			S	SSSS	R					Died 101 days after treatment started
G TE			S	S	R					Died 100 days after treatment started
C CO		O	O	OO		O R*				
P BU			S	SO	OOOS	0000	O	S	OOS	Second course of therapy started at end of 7th month. Cultures subsequent to 8th month negative

O—Negative culture  
S—Sensitivity < 2 mcg./c.c.  
I—Intermediate sensitivity.  
R—Resistant > 500 mcg./c.c.  
\*—Postmortem culture

Seven of the 10 patients with hematogenous infections also had tuberculous meningitis. The in vitro streptomycin sensitivities of the organisms obtained from the cerebrospinal fluids of these seven patients and from the two others who did not have hematogenous tuberculosis are presented in table 3.

The results are essentially the same as those observed in the systemic infections. The appearance of in vitro resistance was noted in all three in whom the organisms persisted in the cerebrospinal fluid. At the time the phenomenon appeared, organisms obtained from the systemic infections of these three individuals were similarly resistant to streptomycin in vitro. It is noteworthy, however, that, in two, the strains first isolated from the cere-

\* In the subsequent discussion the term "streptomycin-resistant" is used to designate strains of bacilli which are not inhibited by 500 micrograms per c.c.

brospinal fluid were drug-sensitive even though organisms from the corresponding systemic infections were highly resistant to streptomycin in vitro. In these two cases, the organisms from the systemic infection had been demonstrably resistant in vitro (insensitive to 500 mcm. per c.c.) for periods of 18 and 46 days when the streptomycin-sensitive bacilli were first isolated from the cerebrospinal fluid. Moreover, in one of these infections, the

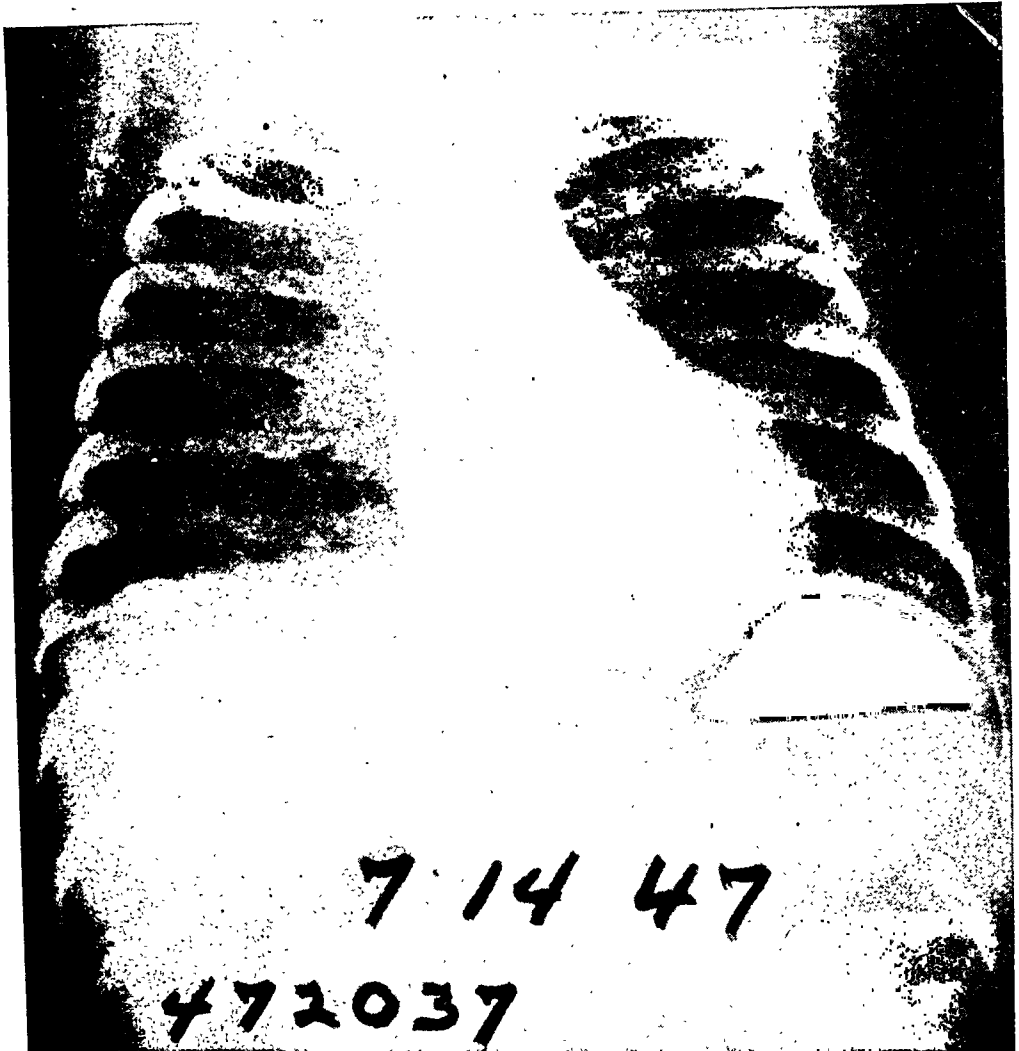


FIG. 6h2.

organisms from the cerebrospinal fluid remained streptomycin sensitive for at least 28 days after the start of the intrathecal administration of the drug.

In these observations, the appearance of drug-resistant bacilli within the central nervous system was not noted until the systemic infection had progressed to a terminal stage. As a result, it was not possible to follow the course of the meningitis itself after the development of drug-resistant (meningeal) organisms. It was also impossible to draw inferences con-

cerning the speed of conversion from drug-sensitive to drug-resistant strains of bacilli because the possibility of terminal reinvasion of the central nervous system by organisms from the systemic infection could not be excluded. For example, in one instance drug-resistant bacilli were first obtained from the

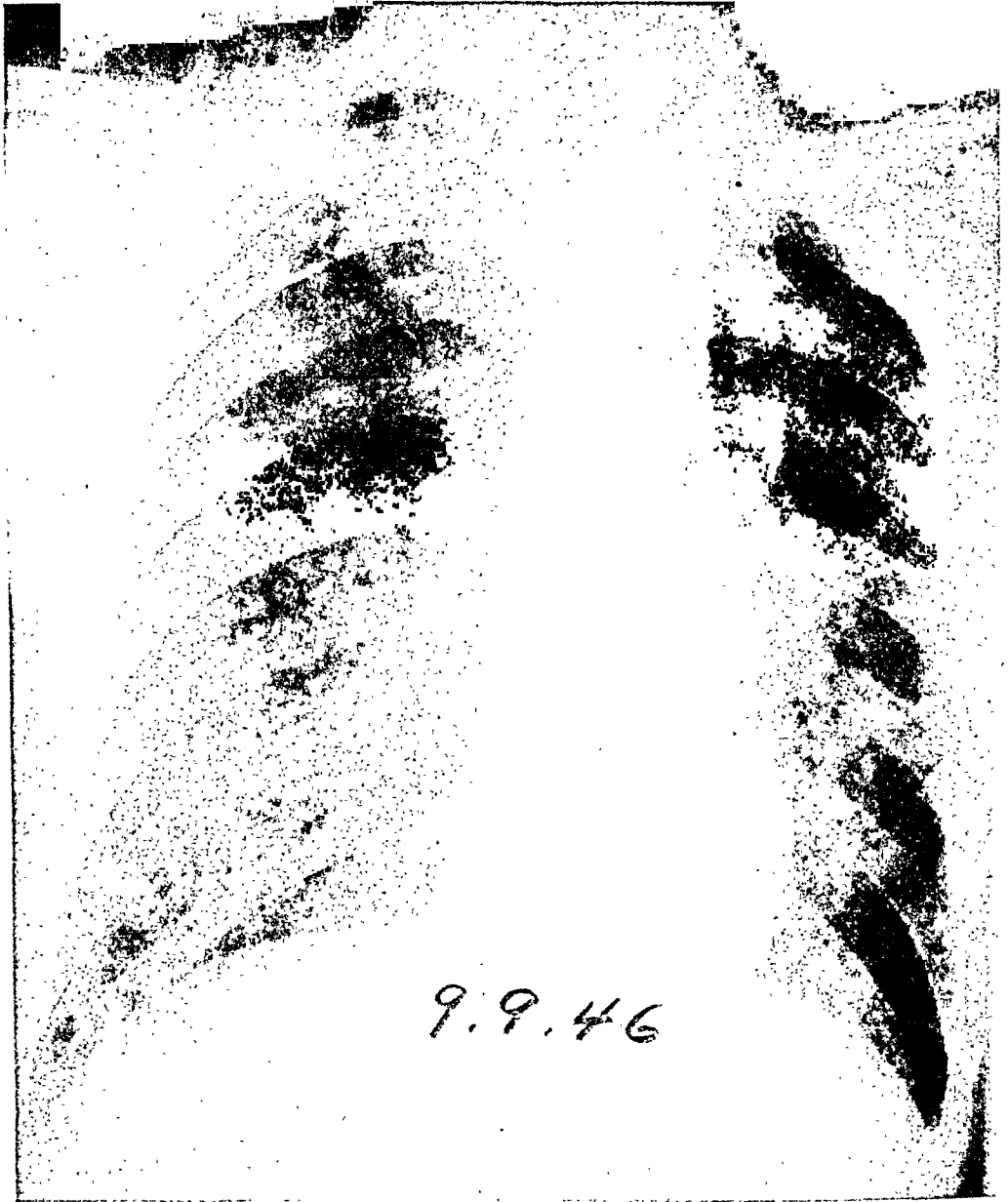


FIG. 611.

cerebrospinal fluid only four days after the isolation of a sensitive strain from the same source. In the 30 days preceding the last isolation of the sensitive strain, 17 similar isolations were also sensitive. As, during the entire period, organisms from the systemic infection were highly resistant, it is

possible that the sudden appearance of drug-resistant bacilli in the central nervous system just before death may have merely represented a recent metastasis.

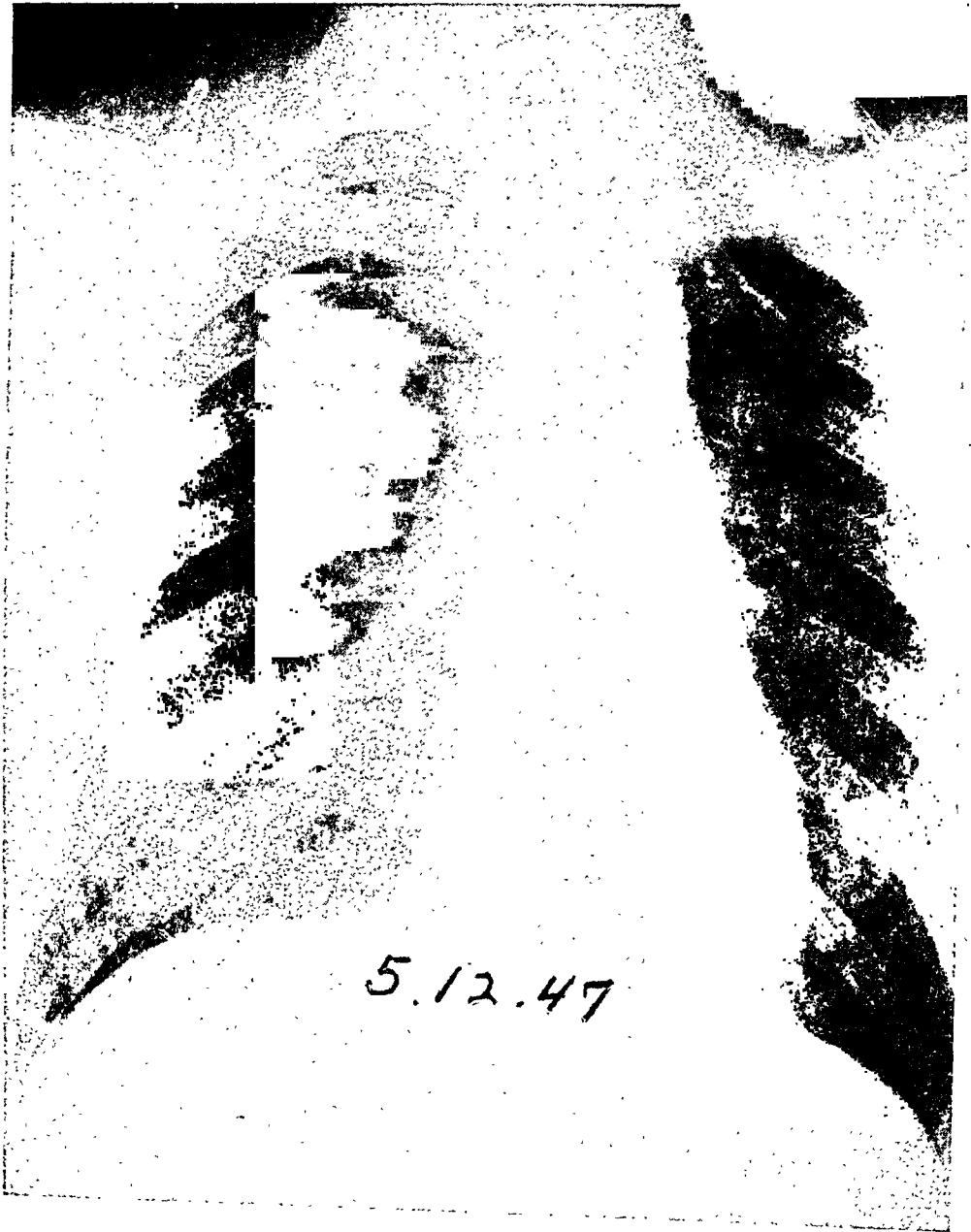


FIG. 6i2.

*Correlation between in Vitro and in Vivo Streptomycin Sensitivity.* In this series of 15 patients with generalized hematogenous tuberculosis, there was a correlation between failure of therapeutic response and the appearance of drug resistance as demonstrable in vitro. Tubercle bacilli which were resistant to streptomycin in vitro were



obtained from a total of four patients with miliary infections. Despite streptomycin therapy, all four of them died as a direct consequence of the miliary disease. During the first one or two months of antimicrobial therapy, before in vitro streptomycin resistance was demonstrable, these four patients presented the same unprecedented clinical, roentgenologic and bacteriologic

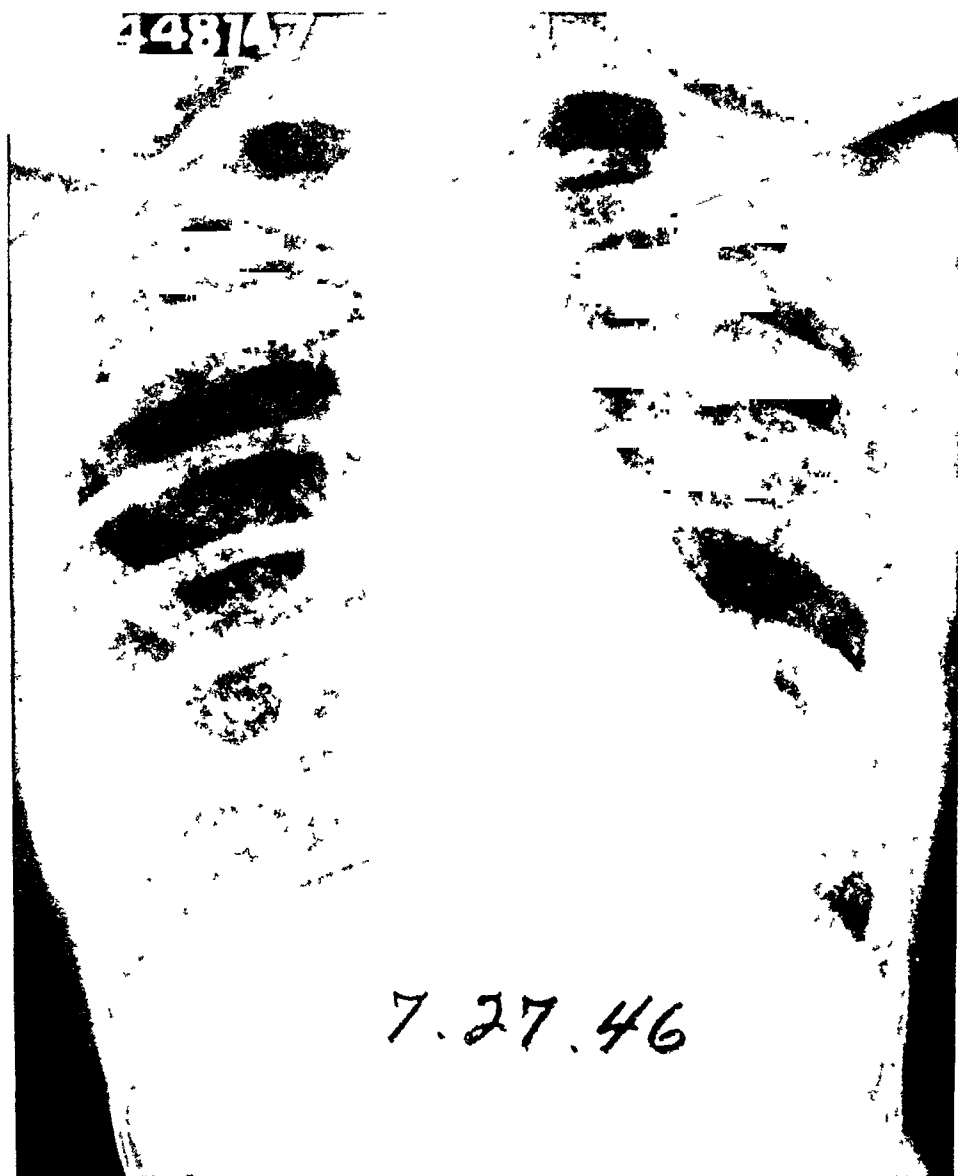


FIG. 6j1.

improvement as was observed in the others whose remissions were sustained. In all four of the patients with drug-resistant bacilli, however, relapse occurred during a period of uninterrupted streptomycin therapy. Moreover, as noted previously, the time of appearance of clinical relapse coincided with the first detection of organisms which were streptomycin-resistant in vitro.

In contrast to the apparent therapeutic response during the early phases of treatment, these relapsing infections were completely uninfluenced by the further administration of streptomycin. In addition to the reappearance of fever, lymphadenopathy, and the characteristic roentgenologic evidences of miliary disease of the lungs, choroidal tubercles developed in one patient and

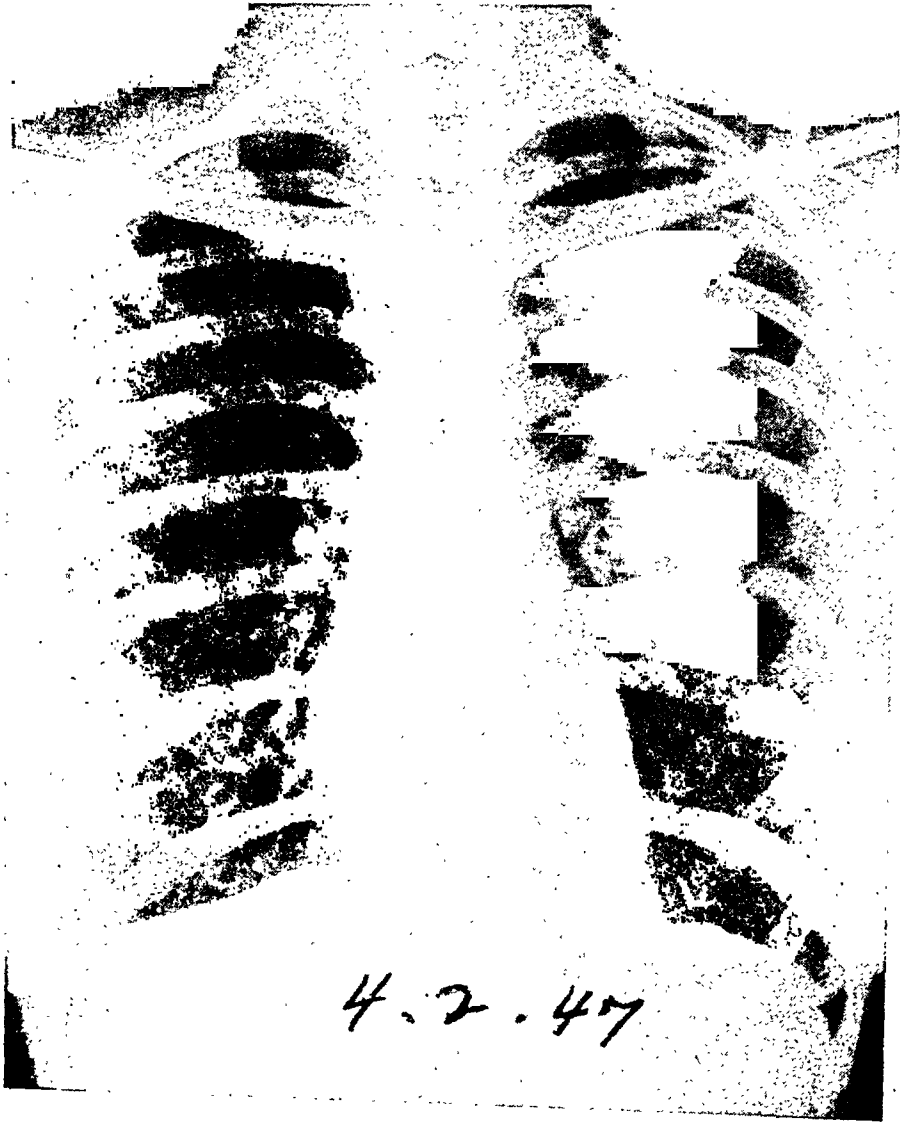


FIG. 6j2.

demonstrable bacteremia in another, despite intensive (three grams daily) streptomycin therapy.

The bacteriologic course of the survivors was in distinct contrast to the findings in the fatal cases. Streptomycin-resistant organisms were never isolated from the five patients who have survived one year after the onset of generalized hematogenous tuberculosis. Moreover, drug-resistant bacilli were never obtained from the two patients whose meningitis is in complete

remission five months after the cessation of therapy. Also in this category is the infant whose miliary tuberculosis was completely healed on postmortem examination (*vide infra*). It should be emphasized, however, that in these seven infections it was not always possible to isolate organisms at any time after the start of treatment, and in no instance were bacilli obtainable later than the sixtieth day of therapy. The remainder of the generalized hema-

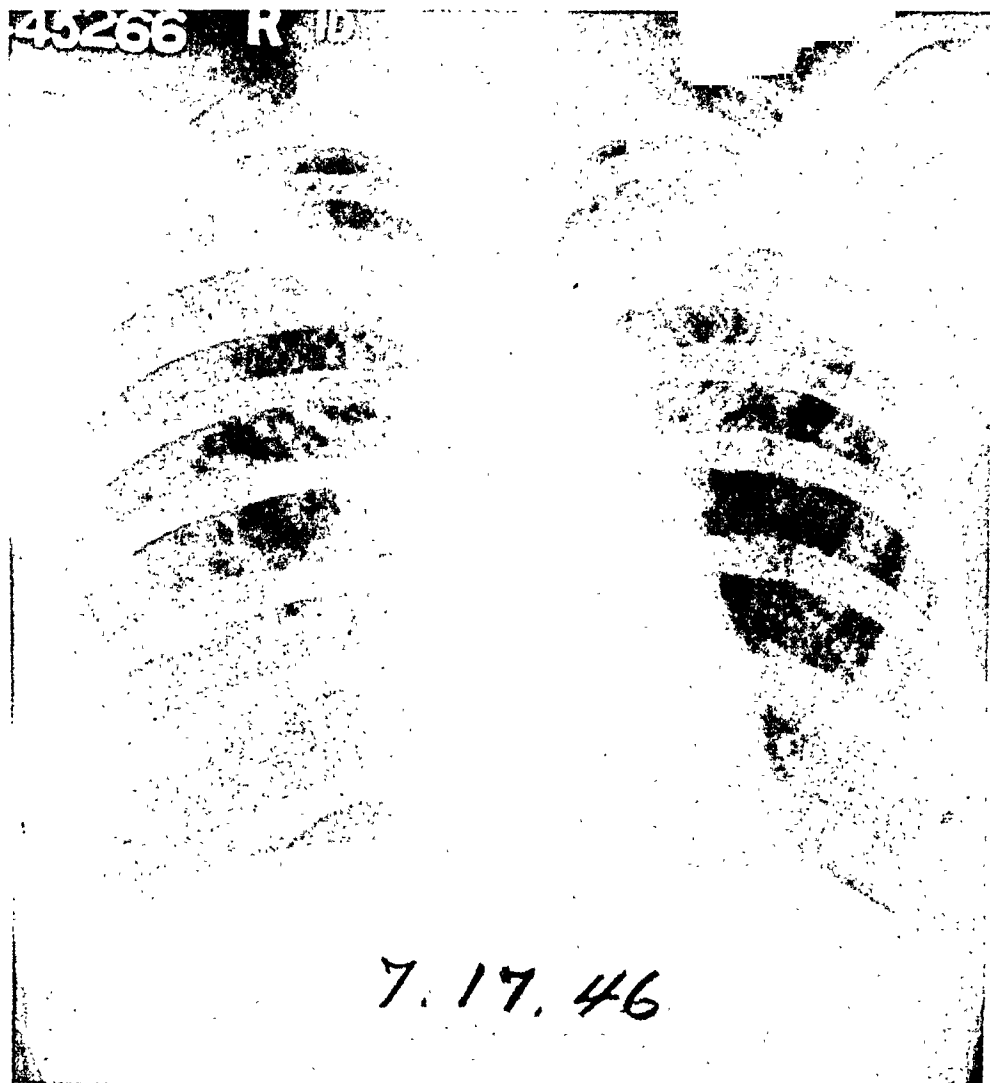


FIG. 6k1.

togenous-meningitis group from whom drug-resistant bacilli were never obtained, consist of three individuals who have completed treatment only recently and the man who died of meningitis on the fortieth day of therapy.

It is of interest that one of the five 12-month survivors, from whom drug-resistant bacilli were never obtained, developed clinical evidences of active tuberculosis two and a half months after the cessation of therapy. Tubercle bacilli could not be cultured from the patient at the time of the

relapse, and the latter appeared to respond satisfactorily to a second course of antimicrobial therapy.

In summary: fatal miliary tuberculosis appeared in all four individuals (with previous miliary disease), from whom drug-resistant bacilli were isolated. Conversely, drug-resistant bacilli were never isolated from the patients with generalized hematogenous tuberculosis or meningitis who eventually attained satisfactory remissions.

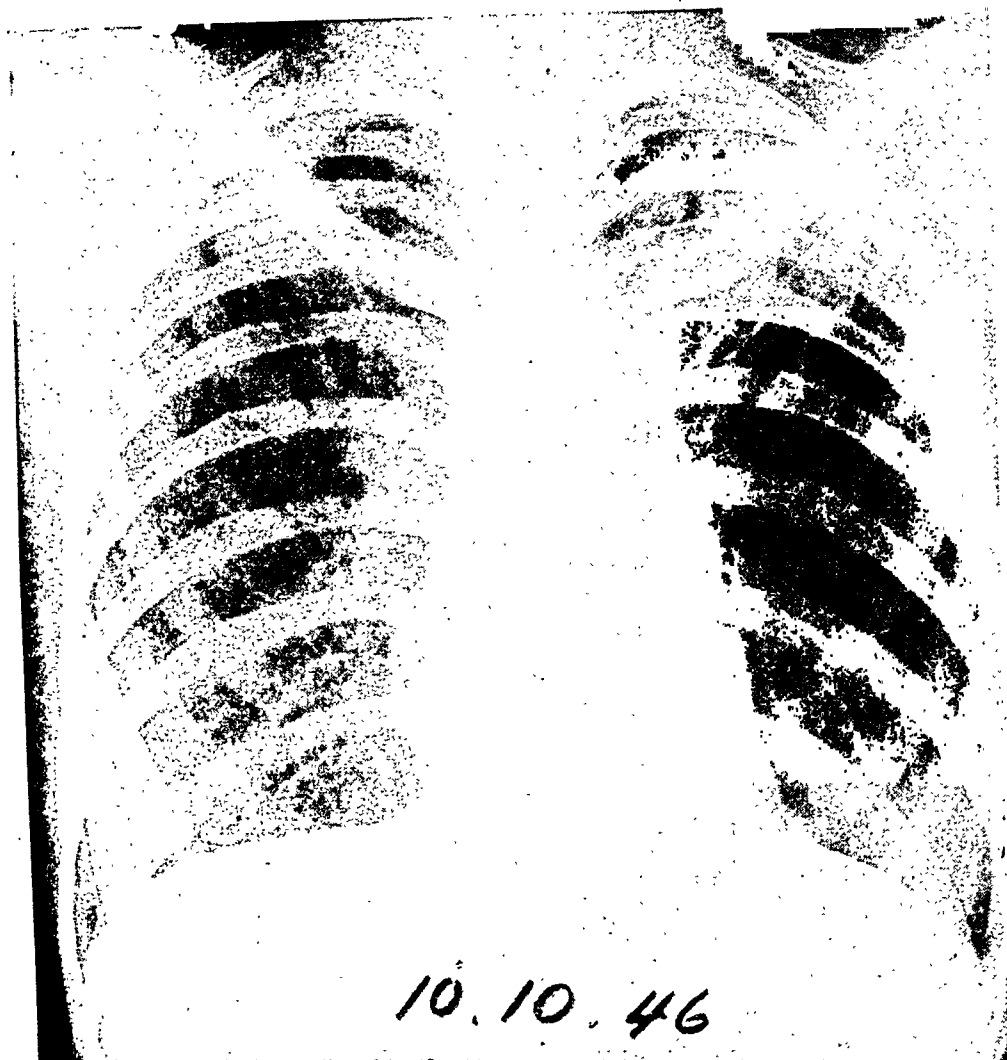


FIG. 6k2.

*Histopathologic Observations.* Postmortem examinations were obtained in six of the seven fatal cases of acute miliary tuberculosis. Two of the patients had experienced only short-lived periods of improvement and had had actively progressing infections associated with streptomycin-resistant bacilli for 30 to 60 days before death. In both cases gross and microscopic examination of the tissues revealed the characteristic changes of tuberculosis. It was not possible to detect histologic traces of the considerable although

temporary regression of the process in the lungs which had occurred several months previously.

Definite evidences of healing were revealed, however, on investigation of the tissues of the patients who had experienced virtually complete remissions at some time during therapy. Moreover, there was evidence of modification of the pulmonary lesions in the tissues of the man who died of meningitis after only 40 days of streptomycin therapy. A detailed description of these findings will be published elsewhere.<sup>16</sup>

The most striking changes were observed in the lungs of the two year old infant (figure 6a) who had died of internal hydrocephalus, 10 months after the original institution of streptomycin therapy for acute miliary tuberculosis. All evidence of the miliary infection had disappeared during the first few months of therapy, and had never returned despite the development of relapsing meningitis.

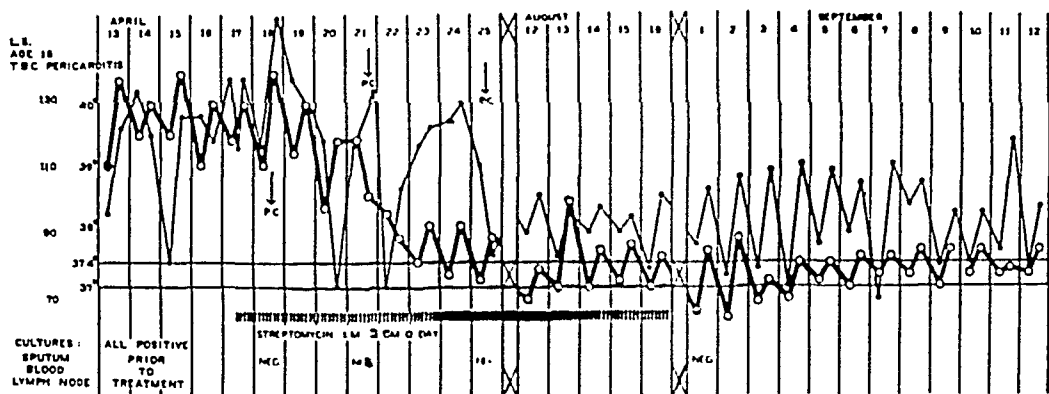


FIG. 7. Patient L. St., tuberculous pericarditis with effusion. Note abrupt defervescence after administration of streptomycin. Vertical arrows indicate pericardeses performed to obtain fluid for streptomycin assays.

On gross inspection of the lungs at postmortem examination, no abnormalities were apparent. Moreover, on low power microscopic examination, the pulmonary tissue appeared to be entirely normal. On examination with greater magnification, however, tiny circumscribed areas of loosely arranged fibrous tissue were observed which were evenly distributed throughout the pulmonary tissue. There were no tubercle bacilli demonstrable in these areas which contained a few lymphocytes but no giant cells or evidence of acute inflammation. In fact, it was impossible to identify the lesions as tuberculous, although they presumably represented the end stage of the miliary tuberculosis which had been demonstrable by roentgenologic and bacteriologic examinations 10 months previously.

A different type of lesion was present in the lungs of a patient who had presented the diphasic type of course described previously. In conformity with the roentgenologic examinations obtained shortly before death, the lungs at post mortem were studded with tubercles. In contrast to characteristic miliary tubercles, however, the lesions observed consisted of three

distinct zones. In the majority of the lesions there was an inner zone of necrotic tissue which was surrounded in whole or in part by a definite ring of fibrous tissue. Outside the ring of fibrous tissue, there was a third ring of active cellular inflammation in which tubercle bacilli were present. Thus it appeared as if partially healed tubercles had broken down to form newly active disease.

*Skin Sensitivity to Tuberculin.* Intracutaneous skin tests (Mantoux) were made at approximately monthly intervals with old tuberculin; 0.001 mg. was given as the first dose and the test repeated with tenfold increases up to 1.0 mg. when necessary. No consistent or significant changes in the degree of sensitivity were noted during or after the streptomycin treatment, except in one case. This patient (figure 6a) with miliary tuberculosis and meningitis, whose generalized systemic infection was apparently cured but who died of hydrocephalus, became negative to doses as high as 2.0 mg.

*Toxicity.* Observations on the toxic effects of the streptomycin regimen in use in this series were made and are presented in detail elsewhere.<sup>7, 10, 14</sup> It is sufficient to state here that all of the important manifestations of toxicity which have been noted following the use of partially purified preparations of streptomycin were also encountered following the use of the highly purified material administered in three gram daily doses.

## DISCUSSION

On the basis of the observations which have been presented, it appears that streptomycin exerts a striking effect upon the course of generalized hematogenous and meningeal tuberculosis. The results are thus in complete agreement with the observations previously reported by Hinshaw and Feldman.<sup>3, 4</sup>

In the present study, evidence of therapeutic activity is afforded by: (1) the uniformity with which the administration of streptomycin was accompanied by marked clinical and roentgenologic improvement; (2) the disappearance of tubercle bacilli from those discharges in which they had been easily demonstrable before therapy; and (3) an impressive degree of healing of the lesions in the lung, as revealed by histologic examination.

Six adults with bacteriologically proved meningitis, miliary, or other generalized hematogenous forms of tuberculosis are in complete remission five to 12 months after the cessation of streptomycin therapy. A seventh individual, though not entirely well, is alive one year after acute miliary tuberculosis and is apparently recovering.

Spontaneous recovery in miliary tuberculosis and in tuberculous meningitis is distinctly unusual. The incidence of apparent recovery reported by Hinshaw and Feldman and encountered in this study is unprecedented and is presumably attributable to the action of the streptomycin.

In contrast to the satisfactory outcome observed in these seven individuals, in another group of seven with miliary tuberculosis, six have died

as a result of their disease and the seventh is not expected to recover. The several months' period of improvement, which appeared soon after the start of streptomycin therapy, was equally striking in both groups. Thus the antimicrobial therapy of tuberculosis is essentially similar to the chemotherapy of other infections. The institution of treatment results in a remission of the infection, permanent in some instances, but followed by relapse in others if the host is unable to maintain control of the infection once antimicrobial action has been withdrawn or ceases to be effective.

In the present study, it appears that the immediate causes of therapeutic failure were the development of drug-resistant strains of tubercle bacilli in four cases and the appearance of meningitis in two.

The fact that tubercle bacilli can be streptomycin-resistant *in vivo* as well as *in vitro* has been established in experimentally infected animals by Feldman et al.,<sup>17</sup> by Youmans and Williston<sup>18</sup> and by Steenken and Wolinsky.<sup>19</sup> These investigators observed, in guinea pigs and in mice, that organisms obtained from treated patients and resistant to streptomycin *in vitro* produced an infection which was uninfluenced by the administration of the drug. It would be difficult to detect the presence of a similar phenomenon in most forms of tuberculosis in humans because of the strong tendency toward natural regression of the infection. In miliary and meningeal tuberculosis, however, the tendency for spontaneous healing is so slight that the development of drug-resistance *in vivo* should be readily apparent if it occurred before the infection was completely controlled by the host. Evidence for this hypothesis is afforded by the course of the patients with relapsing miliary tuberculosis.

In support of the assumption that these four infections were drug-resistant *in vivo* are the following observations: (1) During the first 30 to 90 days of streptomycin treatment, there was an hitherto unprecedented regression which presumably represented an effect of the antimicrobial therapy; (2) Despite the continued administration of the drug, however, there was a reappearance of all of the clinical, roentgenologic and bacteriologic evidences of miliary tuberculosis in four instances, and a similar relapse 17 days after the cessation of therapy in a fifth individual. During relapse, a fresh dissemination of organisms occurred under therapy in at least two patients, as shown by the appearance of bacteremia and choroidal tubercles; (3) Unlike the course displayed in the early phases of treatment, all four of the second bouts of miliary tuberculosis were completely uninfluenced by streptomycin and steadily progressed to a fatal termination; (4) At postmortem examination, bacilli obtained from the lesions were as resistant to streptomycin *in vitro* as the organisms cultured during life; (5) The appearance of relapse coincided in time with the appearance of tubercle bacilli which were highly resistant to the action of streptomycin *in vitro*; (6) Conversely, drug-resistant bacilli were never obtained from the seven individuals who recovered from meningeal, miliary or other forms of generalized hematogenous infections.

In generalized hematogenous tuberculosis, the organisms are so uniformly distributed through the host that bacilli obtained from most of the available sources should be representative of the entire bacterial population. It is conceivable, however, that in occasional instances there will be foci of organisms which have been exposed to appreciably higher or lower concentrations of a drug than is the case for the bacterial population as a whole. In the present study, there were two instances in which bacilli which were sensitive to streptomycin *in vitro* were isolated from the cerebrospinal fluid of individuals who were discharging drug-resistant organisms from other lesions. It is possible that these organisms had remained drug-sensitive within the central nervous system because they had received so little exposure to the drug in the absence of intrathecal administration. Except for infected cerebrospinal fluid, it would not be anticipated that organisms from such "localized" populations would be obtainable for *in vitro* testing. It is probable, therefore, both in miliary and pulmonary tuberculosis, that the bacilli discharged by the host (cerebrospinal fluid excepted) usually constitute representative samples of the bacterial population within the body.

Even if a particular culture represents a fair sample, however, it is usually tested *in vitro* under conditions which favor the growth of only those cells which are resistant to streptomycin. Thus, if only a fraction of the cells of a culture are drug-resistant, the entire culture might appear to be resistant when tested in liquid media. It is not believed that this phenomenon played a significant rôle in the streptomycin-resistance studies of the present investigation. The rate at which the streptomycin-resistant inocula grew, and a few isolated tests in solid media, both indicate that most, if not all, of the cells were streptomycin-resistant in the so-called resistant cultures.

It should also be noted that it is possible to alter the value for the streptomycin-sensitivity of a particular culture by appropriate alterations in the conditions of the test. In the technic used in the present experiments, the concentrations of albumin (0.5 per cent) and of Tween (0.02 per cent) are of the utmost importance. Fisher<sup>20</sup> has recently observed that, in a less rich medium with a low concentration of albumin (0.2 per cent) and a high concentration of Tween (0.05 per cent), falsely low values for the streptomycin sensitivity of tubercle bacilli may be obtained. This albumin-Tween effect is not observed under the conditions of the test employed in this investigation.

The mechanisms by which microorganisms develop resistance to antimicrobial agents are poorly understood.<sup>21</sup> It is possible that there is no unitary explanation of the phenomena, but that several different types of mechanism may be operative. Regardless of which of the currently held explanations of the phenomenon may be correct, it would seem that streptomycin-sensitive bacteria will eventually become streptomycin-resistant if they are continuously or repeatedly exposed to the drug in a situation in which complete healing or arrest of the lesion fails to occur. It is by no means clear whether the bacteria which remain within the host after ap-



parent arrest of the lesions also become drug-resistant, but there is reason to believe that they may not. In two instances in the present series, lesions which healed under therapy, and hence discharged no demonstrably resistant tubercle bacilli, relapsed three to four months later and were apparently still susceptible to the effects of streptomycin. Moreover, Karlson and Feldman have recently observed,<sup>17</sup> in guinea pigs purposely treated with low doses of streptomycin, that the organisms isolated from grossly healed lesions were sensitive to streptomycin in vitro. In contrast, the tubercle bacilli obtained from macroscopically unhealed lesions were highly resistant to the action of the drug in vitro. In four of the five instances in the present study in which bacilli were obtained after the second month of therapy, the organisms were drug-resistant in vitro. In the fifth case (also a fatality) equivocal results were observed on in vitro testing of the only culture obtainable.

The high incidence of bacterial resistance when unhealed lesions are present for more than a few months of therapy creates a therapeutic dilemma in the treatment of miliary tuberculosis. The goal of antimicrobial therapy is to establish control of an infection for a sufficiently long period to afford opportunity for the host to mobilize mechanisms for permanent control. The very fact that generalized hematogenous tuberculosis becomes established at all indicates either that the usual mechanisms for the localization of tuberculous infection are not operative or that a purulent focus has unusually direct and continuing access to a major vascular channel. In either of these situations, in order to avoid relapse, it would be necessary to maintain antimicrobial therapy for a much longer period than would be required for a process already localized by the host to an area of lung. Thus in the treatment of miliary tuberculosis, it would seem reasonable to continue streptomycin therapy uninterruptedly and for as long as possible. If this procedure is followed, however, relapse with drug-resistant organisms is apt to occur unless a considerable degree of healing occurs during the first few months of treatment. The observations of Miller and Bohnhoff<sup>22</sup> and of Hall and Spink<sup>23</sup> on *Meningococcus* and *B. abortus* are disturbing in this connection for they suggest the possibility that continuation of streptomycin in the presence of drug-resistant organisms might actually enhance the pathogenicity of the latter.

Until more information is available, it seems advisable to choose the lesser of two evils by limiting the period of streptomycin therapy to only six or eight weeks. Although this procedure might increase the chance of post-treatment relapse, it should appreciably decrease the risk of relapse with streptomycin-resistant organisms.

The complication of meningitis which was apparently responsible for two of the failures in therapy presumably arose from foci which were present in the brain before therapy, and which slowly evolved to the point of recognition while the drug was being administered by the intramuscular route. In support of this assumption is the fact that the concentrations of streptomycin attained in the nervous system following intramuscular administration are

notably low. Moreover, it is unlikely that blood-borne metastasis to the brain would occur at the time of the most rapid regression of the other miliary lesions.

The development of meningitis considerably complicates the antimicrobial therapy of any infection, tuberculous or otherwise. It is by no means clear why invasion of the central nervous system by members of a particular bacterial species results in an illness which is so much less amenable to treatment than the infections produced elsewhere by the same organisms. It is unlikely that the phenomenon can be explained wholly if at all on the basis that the various drugs fail to penetrate the central nervous system in sufficient concentration. It seems much more reasonable to believe that the natural mechanisms by which the body destroys tubercle bacilli and certain other bacteria such as pneumococcus, are considerably less efficient within the central nervous system or other body compartments than they are in the lung. It is probable that the natural mechanisms for the removal of necrotic tissue and the repair of diseased areas are also less efficient in the body compartments. Without the operation of these natural mechanisms for the eradication of bacteria, and repair of the lesions, the effectiveness of antimicrobial therapy is considerably impaired. Thus in tuberculous meningitis as in pneumococcus meningitis, there will be a high incidence of therapeutic failure despite the availability of powerful antimicrobial agents.

From the experience in the present series of nine patients, there are indications that the chance of a successful therapeutic result in tuberculous meningitis might be greater when the meningitis is not accompanied by acute generalized hematogenous tuberculosis. When the meningitis arises in association with a generalized infection, there is the possibility of developing a drug-resistant systemic infection which dominates the total illness. Moreover, the chance that multiple foci are present within the brain is much more likely. Conversely, in tuberculous meningitis without generalized hematogenous infection, there is a possibility that only a single focus is concerned, and hence a therapeutically induced remission might be less likely to be followed by relapse.

The rapid defervescence and disappearance of clinical toxicity, which followed the institution of therapy in the majority of the generalized hematogenous infections, was a most striking and provocative phenomenon. At times (figure 4a) the appearance of the phenomenon was so rapid and abrupt as to resemble the crisis of pneumococcus pneumonia. The mechanism by which the phenomenon occurs in tuberculosis is not at all clear. It is generally believed that invasion of unsensitized tissue by *M. tuberculosis* does not produce fever and the other evidences of systemic toxicity.<sup>24</sup> Presumably, these phenomena arise as a consequence of the reaction of previously sensitized tissue to products derived from tubercle bacilli. The products, which are not harmful to human tissue in the absence of prior sensitization, are released from dead organisms and are also elaborated to an unknown extent by living bacilli. So far as is known, streptomycin acts only on the

living tubercle bacilli and is chiefly effective on actively multiplying cells.<sup>25</sup> There is no evidence that the drug reacts with the bacillary products which are presumed to be responsible for the production of clinical toxicity. Nevertheless, the introduction of streptomycin results in a prompt disappearance of the systemic manifestation of toxicity, and the phenomenon occurs despite the persistence of the capacity to react to the particular products of the bacillus used in testing the skin reactions to tuberculo-protein.

It is difficult to explain streptomycin-induced crisis if the principal cause of toxicity, in sensitized individuals, is a product of dead organisms. Even if it be assumed that the drug drastically lowers the bacterial population and thus reduces the number of cells eventually available for autolysis, it would be anticipated that during the period of such a rapid reduction an intensification of toxicity might occur. It seems much more likely that the production of toxicity is directly related to the presence of actively growing bacterial cells. Thus the rapid disappearance of clinical toxicity would be the result of a sudden drug-induced interruption of bacterial growth and multiplication rather than a consequence of the neutralization of autolytic products.

The usual range of the multiplication-time of tubercle bacilli *in vivo* is not known, and presumably varies considerably with the intensity of the infection. Youmans has found, however, that the usual range of multiplication-time for organisms growing in a liquid synthetic medium is 36 to 72 hours.<sup>26</sup> It is of interest to compare this value with the 72 to 96 hour period required for the disappearance of signs of toxicity in the present series of clinical infections.

The questions raised by this phenomenon of streptomycin-induced crisis have important implications in regard to the pathogenesis of tuberculosis and its relation to antimicrobial therapy. It is to be hoped, therefore, that the subject will receive considerable further investigation.

Another phenomenon worthy of mention is the rapid reduction of the size of the cardiac silhouette during the first two weeks' treatment of three patients with miliary tuberculosis. It is assumed that this phenomenon represented the resorption of a pericardial effusion or the disappearance of a considerable degree of cardiac dilatation. In no instance, however, was there any clinical evidence of the presence of either of these two complications.

From the results of the present investigation, it may be seen that in the streptomycin treatment of generalized hematogenous tuberculosis there are so many unsettled questions which pertain to the parasite or to the host, that it is impossible to outline an ideal chemotherapeutic regimen at this time. The results which have been presented were observed on a regimen of 3.0 grams of streptomycin daily, administered continuously for a period of three or four months. This regimen was chosen arbitrarily in an attempt to afford the maximum therapy, presumed to be compatible with safety, over the longest period of time which would be generally practicable. It is conceivable that the high incidence of one cause of failure, the appearance of

drug-resistant strains of bacilli, might be related to the length of the total period of therapy. At least it can be stated that the appearance of drug-resistance was not prevented by what is, in effect, the maximal tolerated regimen. Accordingly, an investigation of the use of a lower daily dose (one gram) for a period of six to eight weeks is in progress, and will be reported at a later date.

### SUMMARY

The administration of streptomycin to 17 patients with bacteriologically proved meningeal, miliary or other types of generalized hematogenous tuberculosis was followed; in every instance, by a striking alteration in the course of the infection. Six of these individuals (meningitis, two; \* miliary, two; and other forms of generalized hematogenous disease, two) have attained complete remissions which have been maintained for five to 12 months after the completion of therapy. A seventh patient is apparently recovering one year after an acute miliary infection. Another seven individuals, all with miliary disease, have died as a consequence of their infection. The remaining three patients have only recently completed therapy. Meningitis was present, or appeared during therapy, in seven of 13 patients with miliary tuberculosis, but was the principal cause of death in only two instances. In every one of four patients from whom bacilli resistant to streptomycin in vitro were obtained, the miliary infection resumed a progressive course which terminated fatally despite further streptomycin therapy. Histologic and bacteriologic examination of the tissues of six of the fatal cases revealed changes which could be correlated with the clinical, bacteriologic and roentgenologic status of the infections at the time of death.

### CONCLUSIONS

1. In meningeal and generalized hematogenous tuberculosis, the administration of streptomycin results in a remission of the infection, permanent in some instances, but followed by relapse in others when the antimicrobial action is no longer exerted.
2. In generalized hematogenous tuberculosis, the appearance of tubercle bacilli which are resistant to the action of streptomycin in vitro reflects the presence of a drug-resistant infection in vivo.

### BIBLIOGRAPHY

1. SCHATZ, A., BUGIE, E., and WAKSMAN, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria, *Proc. Soc. Exper. Biol. and Med.*, 1944, *lv*, 66-69.
2. FELDMAN, W. H., and HINSHAW, H. C.: Effects of streptomycin on experimental tuberculosis in guinea pigs: A preliminary report, *Proc. Staff Meet., Mayo Clinic*, 1944, *xix*, 593-599.

\* One of these patients has developed a clinical and bacteriologic relapse since the printing of this report.

3. HINSHAW, H. C., and FELDMAN, W. H.: Streptomycin in treatment of clinical tuberculosis: A preliminary report, Proc. Staff Meet., Mayo Clinic, 1945, xx, 313-318.
4. HINSHAW, H. C., FELDMAN, W. H., and PFEUTZE, K. H.: Treatment of tuberculosis with streptomycin, Jr. Am. Med. Assoc., 1946, cxxxii, 778-782.
5. HINSHAW, H. C., PYLE, M. M., and FELDMAN, W. H.: Streptomycin in tuberculosis, Am. Jr. Med., 1947, ii, 429-435.
6. MUSCHENHEIM, C., MCDERMOTT, W., HADLEY, S. J., HULL-SMITH, H., and TRACY, A.: Streptomycin in the treatment of tuberculosis in humans. II. Pulmonary tuberculosis, Ann. Int. Med. (To be published.)
7. FARRINGTON, R. F., HULL-SMITH, H., BUNN, P. A., and MCDERMOTT, W.: Streptomycin toxicity: Reactions to highly purified drug on long continued administration to human subjects, Jr. Am. Med. Assoc., 1947, cxxxiv, 679-688.
8. FRIED, J., and TITUS, E.: Streptomycin B, an antibiotically active constituent of streptomycin concentrates, Jr. Biol. Chem., 1947, clxviii, 391-392.
9. HOBBY, G., and LENERT, T. F.: Biological activity of a residual form of streptomycin against *Eberthella typhosa*, Proc. Soc. Exper. Biol. and Med., 1947, lxxv, 249-254.
10. MCDERMOTT, W.: Toxicity of streptomycin, Am. Jr. Med., 1947, ii, 491-500.
11. DUBOS, R. J., and DAVIS, B. D.: Factors affecting the growth of tubercle bacilli in liquid media, Jr. Exper. Med., 1946, lxxxiii, 409-423.
12. STEBBINS, R. B., and ROBINSON, H. J.: A method for determination of streptomycin in body fluids, Proc. Soc. Exper. Biol. and Med., 1945, lix, 255.
13. BOXER, G. E., JELINEK, V. C., and LEGHORN, P. M.: The colorimetric determination of streptomycin in clinical preparations, urine, and brain, Jr. Biol. Chem., 1947, clxix, 153.
14. STEVENSON, L. D., ALVORD, E. C., JR., and CORRELL, J. W.: Degeneration and necrosis of neurones in eighth cranial nuclei caused by streptomycin, Proc. Soc. Exper. Biol. and Med., 1947, lxxv, 86-88.
15. National Tuberculosis Association: Diagnostic Standards and Classifications of Tuberculosis, 1940, New York.
16. FLOREY, C., KIDD, J., MCDERMOTT, W., and MUSCHENHEIM, C.: To be published.
17. KARLSON, A. G., and FELDMAN, W. H.: Resistance of tubercle bacilli to streptomycin in guinea pigs after administration of the drug: The effect on response to treatment with streptomycin, Abstr. Proc. Soc. Am. Bacteriologists, Philadelphia, May 1947, pg. 67.
18. YOUMANS, G. P., and WILLISTON, E. H.: Effect of streptomycin on experimental infections produced in mice with streptomycin resistant strains of *M. tuberculosis* var. *hominis*, Proc. Soc. Exper. Biol. and Med., 1946, lxiii, 131-134.
19. STEENKEN, W., JR., and WOLINSKY, E.: Personal communication.
20. FISHER, M. W.: Personal communication.
21. SELBIE, F. R.: Microbial resistance to chemotherapeutic drugs, Brit. Med. Bull., 1946, iv, 267.
22. MILLER, C. P., and BOHNHOFF, M.: Observations on the development of streptomycin resistance by meningococcus. Presented at Conference on Antibiotic Research held at Washington, D. C., on January 31 and February 1, 1947, under the auspices of the Antibiotics Study Section, National Institute of Health.
23. HALL, W. H., and SPINK, W. W.: In vitro sensitivity of brucella to streptomycin: Development of resistance during streptomycin treatment, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 403-406.
24. RICH, A. R.: The pathogenesis of tuberculosis, 1944, Charles C. Thomas, Springfield, Illinois.
25. MIDDLEBROOK, G., and YEGIAN, D.: Certain effects of streptomycin on mycobacteria in vitro, Am. Rev. Tuberc., 1946, liv, 553-558.
26. YOUMANS, G. P.: A method for the determination of the culture cycle on the growth rate of virulent human type tubercle bacilli, Jr. Bacteriol., 1946, li, 703-710.

# CASE REPORTS

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## PRIMARY CARCINOMA OF THE GALL-BLADDER IN A PATIENT WITH CONGENITAL HEMOLYTIC JAUNDICE\*

By HENRY G. HAGER, JR., M.D., *Williamsport, Pennsylvania* and  
WESLEY VAN CAMP, M.D.,† *Pueblo, Colorado*

### INTRODUCTION

CONGENITAL hemolytic jaundice and primary carcinoma of the gall-bladder are both relatively rare diseases. The occurrence of the two in our patient was probably not a mere coincidence—the former condition was undoubtedly indirectly responsible for the later fatal disease. It was because of this probable etiological sequence of events (congenital hemolytic jaundice → cholelithiasis at an early age → primary carcinoma of the gall-bladder and death at 36 years of age) that we are reporting this unusual case.

### CASE REPORT

A white, 36 year old coast guardsman was admitted to the U. S. Marine Hospital, Kirkwood, Missouri, on October 16, 1945, with the complaints of weakness, loss of weight, loss of appetite and slight upper abdominal pain of one month's duration.

*Present Illness.* During the latter part of August, 1945 the patient began to feel weak. During September, 1945 he did not feel up to par but had no localized complaints. On October 7, 1945, while home on leave, he developed fever, nausea, anorexia, and marked weakness. He had lost about 30 pounds. He went to bed and remained there for seven days, when he reported to the medical officer and was ordered to the hospital.

*Family History.* Father died accidentally. Mother and sister well. There was no history of blood dyscrasia in the family.

*Past History.* He had served in the South Pacific for two years until April, 1945. Typhoid fever at age twelve. In June, 1933 he had a splenectomy for congenital hemolytic jaundice of eight years' duration.‡ The removed spleen was four times normal size and showed increased fibrosis and hyperplastic splenitis. At this operation the gall-bladder was noted to contain many small stones. Six months post-operatively he was apparently well. The jaundice had disappeared, as evidenced by the Van den Bergh reaction which was positive indirect, 0.28 mg. per cent. The red cells still showed slightly increased fragility.

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From the Medical and Surgical Departments, U. S. Marine Hospital, Kirkwood, Missouri.

† At the time this article was written both authors were on active duty in the Reserve Corps of the United States Public Health Service. This article was approved for publication by the Surgeon General of the USPHS.

‡ We wish to thank Dr. G. O. Broun, Medical Director of Firmin Desloge Hospital, for allowing us to review in detail the record of our patient's hospitalization in 1933 at that institution.

*Physical Examination.* The patient was 66 inches in height and weighed 137½ pounds. The temperature on admission was 101° F., the pulse rate was 100, and the blood pressure was 110 mm. Hg systolic and 70 diastolic. He was a young white male who appeared slightly jaundiced. There was a slight icteric tinge of the sclerae. The abdomen was rounded and soft. There was a large curved, well healed scar on the left side of the abdomen. There was slight tenderness in the right upper quadrant, and the liver edge was palpable 2 cm. below the costal margin. Otherwise, the examination was negative. A tentative diagnosis of catarrhal jaundice was made.

*Laboratory Studies.* The hemoglobin was 85 per cent; the red cell count was 4,160,000, and the white cell count was 15,000. The differential count was normal, showing 72 per cent neutrophils. Repeated urinalyses were negative except for a trace of albumin. The icteric index was 6.6 and 6.0 on consecutive days. The blood sedimentation rate was greatly increased, reaching 23.5 mm. in 20 minutes. Blood culture was reported negative on October 20 and was again negative on October 25. Agglutination tests were reported negative for *B. abortus*, *P. tularensis* and *S. paratyphi A*. Agglutination was obtained with *E. typhosa* antigen in 1:80 dilution and with *S. paratyphi B* antigen in 1:160 dilution. Stool examinations were negative for parasites, and the culture produced *E. coli*. The red cell fragility range was .471 to .300 with a method which gives a normal range of .412 to .300. Roentgen-ray examination of the chest was entirely negative. The cholecystogram showed numerous small gall stones but no evidence of filling of the gall-bladder with the dye.

*Clinical Course During Preoperative Period.* The patient had a continued fever ranging from 100 to 103.6° F. He evidenced very little distress except for malaise and slight soreness in the right upper quadrant. The initial diagnosis was ruled out by the normal icteric index. He had received booster shots for typhoid and paratyphoid every year for three years, and so the positive agglutination tests were not thought to be significant. A tentative diagnosis of abdominal Hodgkin's disease was made. On October 25, because infection could not be ruled out, and because the white cell count had risen to 25,000, he was started on 50,000 unit doses of penicillin every three hours. It was discontinued on November 1, 1945. There had been no effect upon the patient's general condition nor upon the temperature range. On this day there was slight tenderness in the right upper quadrant, and the liver was palpable 3 cm. below the costal margin. There appeared to be a rounded irregularity of the liver edge. A sternal biopsy was obtained which showed large clumps of normally cellular marrow. There was a normal distribution of erythroid and myeloid elements, but some of the myelocytes showed toxic granules, and there was a slight shift to younger forms. The findings were thought to be compatible with a chronic infection or a chronic disease such as Hodgkin's disease.

The fever continued, varying from 101 to 104°. The white cell count rose to 32,000 while the hemoglobin fell to 60 per cent and the red cell count to 3,900,000. There were no further symptoms, nor were there any further physical findings except for progressive loss of weight and strength.

*Operation.* Exploratory laparotomy was done on December 3, 1945, using continuous spinal anesthesia. The peritoneal cavity contained a large amount of clear amber fluid. The gall-bladder was thickened and indurated, under great tension, and almost completely surrounded by omental adhesions. The liver was enlarged and studded with innumerable nodules varying in size from 1 mm. to 2 cm. These nodules were hard, of a pale yellowish color, and had the gross appearance of carcinoma. No further extensions were found. The spleen was absent, and there were numerous adhesions at its former site. When the gall-bladder was opened, approximately 200 black gall stones, varying in size from 5 mm. to 1 cm., were found and removed. At one point the gall-bladder had perforated into the liver. A friable, cauliflower-like growth involved the gall-bladder mucosa. A section of the fundus

of the gall-bladder was removed for histologic study, and a drain was sewn into the gall-bladder. A liver biopsy was obtained.

*Histopathologic Report.* The liver was practically replaced by large pale staining cells with large nucleoli, well defined nuclear membranes, and polyhedral cytoplasm. Mitoses were frequent. There was no differentiation as to histogenic structure, except that there was some attempt at adenomatous formation. The adjoining liver cells showed extreme atrophy and congestion of the sinusoids. There was considerable deposit of pigment in the Kupffer cells. The gall-bladder wall showed extreme hyalinization, and in one small area the same type tumor as was found in the liver was present.

*Diagnosis.* Carcinoma of the gall-bladder and liver, chronic cholecystitis, and cholelithiasis.

*Postoperative Course.* Following operation the temperature chart continued to show the same type and degree of elevation as before operation. Large quantities of ascitic fluid drained for several days, but at no time did bile appear on the dressings. The wound healed well, and the drain and sutures were removed on the ninth day. Jaundice became evident a few days after operation and increased rapidly. Edema of the lower extremities and dependent portions of the trunk developed on the fifteenth day. He gradually became weaker and died at 12:20 p.m. on January 4, 1946, 32 days after operation.

*Autopsy.* Autopsy was done at 3:30 p.m., January 4, 1946. The principal finding was primary carcinoma of the gall-bladder with massive metastases in the liver, especially in the right lobe. There was no evidence of pulmonary disease or metastases. There was a large amount of free fluid in the thorax and the peritoneal cavity. No evidence of carcinoma was found in any portion of the body except in the gall-bladder, the liver, and the adherent omentum. Microscopic examination of the tissues revealed epidermoid carcinoma.

## REVIEW OF LITERATURE

The incidence of gall stones in congenital hemolytic jaundice listed in several standard texts of hematology<sup>1</sup> has been variously estimated from 60 to 70 per cent of cases. Gall stones occur at a much younger age in people with this condition than in the general population and many instances of cholelithiasis in early childhood have been reported.<sup>2</sup>

Estimates of the percentage of the general population that have cholelithiasis would be very speculative since "gall stone surveys" of large representative sections of our population have never been made. The incidence has been suggested to be somewhere between 10 and 20 per cent of adults<sup>3</sup>—definitely higher in females.

Thus the incidence of gall stones is three to six times higher in congenital hemolytic jaundice than in the population as a whole, and gall stones appear at a much earlier age.

The exact rôle of gall stones in the etiology of primary carcinoma of the gall-bladder is still obscure. Ewing<sup>4</sup> in reviewing the literature, quotes several authors who found cholelithiasis in 70 to 100 per cent of cases of primary carcinoma of the gall-bladder. He considered the remarkable etiological relation with cholelithiasis as one of the most interesting features of the disease.

While experimental evidence is definitely lacking<sup>5</sup> the consensus of contemporary clinicians was expressed by Bockus<sup>3</sup> in the following statement: "Statistical studies suggest that antecedent calculous cholecystitis has an im-



portant relationship to the occurrence of cancer of the gall-bladder." Most pathologists<sup>6</sup> concur with this opinion.

Graham<sup>7</sup> in 1931 was among the first to recommend cholecystectomy in all cases of gall stones—with or without symptoms—to prevent the development of carcinoma. Although all subsequent writers<sup>8</sup> do not agree, the majority of recent papers<sup>9</sup> urge cholecystectomy for almost all calculous gall-bladders as the only means of reducing the incidence and mortality rates for primary carcinoma of the gall-bladder.

Horne<sup>10</sup> recently reported two cases of congenital hemolytic jaundice with non-malignant gall-bladder complications requiring surgical treatment. In reviewing this problem he concluded that cholecystitis and cholelithiasis are frequent complications, and he advised cholecystectomy in all cases of congenital hemolytic jaundice when gall stones are present. This may be done at the time of splenectomy or later.

It is not in the province of this paper to discuss the efficacy of splenectomy in congenital hemolytic jaundice; however, it is of interest to note the following facts in this case. Splenectomy permanently alleviated the jaundice which had been present for about eight years. However, 13 years after splenectomy the increased erythrocyte fragility was still present.

To our knowledge this is the first report of a case of primary carcinoma of the gall-bladder in a case of congenital hemolytic jaundice. It is hoped that this report may stimulate the reporting of any similar cases and that it may possibly help to prevent other patients from developing this rare and fatal complication.

### SUMMARY AND CONCLUSIONS

A case of primary carcinoma of the gall-bladder in a patient with congenital hemolytic jaundice is presented.

The etiological relationship of the two diseases is discussed. Congenital hemolytic jaundice caused gall stones at an early age in our patient. The presence of gall stones for over 12 years was probably a contributing factor in the development of malignancy.

Since non-malignant gall-bladder complications are frequent in patients with congenital hemolytic jaundice, the possibility of developing malignancy is an additional reason for cholecystectomy in these patients when gall stones are present.

*Note:* We wish to thank Dr. Nathan A. Womack, Dr. Carl V. Moore, and Dr. David E. Smith for their clinical and laboratory studies of the patient.

### BIBLIOGRAPHY

1. FOWLER, W. M.: Hematology, 1945, Paul B. Hoeber & Co., New York.  
KRACKE, R. R.: Diseases of the blood, 2nd Edition, 1941, J. B. Lippincott Co., Philadelphia.
2. DOWNEY, HAL, Editor: Handbook of hematology, 1938, Vol. iii, Paul B. Hoeber & Co., New York.
- WINTROBE, M. M.: Clinical hematology, 1942, Lea & Febiger, Philadelphia.
2. BROOKS, C. D., CLINTON, W. R., and ASHLEY, L. B.: Congenital hemolytic icterus with cholelithiasis, *Am. Jr. Surg.*, 1935, xxix, 319.

- DIAMOND, L. K.: Congenital hemolytic anemia in infancy and childhood, *Med. Clin. N. Am.*, 1937, xxi, 401.
- GAIRDNER, DOUGLAS: The association of gallstones with acholuric jaundice in children, *Arch. Dis. Child.*, 1939, xiv, 109.
3. BOCKUS, H. L.: *Gastroenterology*, 1946, Vol. iii, W. B. Saunders Co., Philadelphia.
- ROBERTSON, H. E.: Silent gallstones, *Gastroenterology*, 1945, v, 345.
4. EWING, JAMES: *Neoplastic diseases*, 1946, W. B. Saunders Co., Philadelphia.
5. BURROWS, HAROLD: An experimental inquiry into the association between gall stones and primary carcinoma of the gall-bladder, *Brit. Jr. Surg.*, 1933, xx, 607-629.
- BURROWS, HAROLD: Gall stones and cancer: a problem of aetiology, with special reference to the role of irritation, *Brit. Jr. Surg.*, 1939, xxvii, 166.
6. MOORE, R. A.: *Textbook of pathology*, 1944, W. B. Saunders Co., Philadelphia.
- BOYD, WILLIAM: *Surgical pathology*, 5th Edition, 1942, W. B. Saunders Co., Philadelphia.
- KAUFMANN, EDWARD (Translated by REIMANN, STANLEY): *Pathology*, 1929, P. Blakiston's Son & Co., Philadelphia.
- BELL, E. T.: *Textbook of pathology*, 5th Edition, 1944, Lea & Febiger, Philadelphia.
- KARSNER, H. T.: *Human pathology*, 6th Edition, 1942, J. B. Lippincott Co., Philadelphia.
7. GRAHAM, E. A.: The prevention of carcinoma of the gall-bladder, *Ann. Surg.*, 1931, xciii, 317.
8. COLE, W. H.: *Textbook of surgery*, in Christopher's 4th Edition, 1945, W. B. Saunders Co., Philadelphia.
- WARREN, RICHARD, and BALCH, F. G., JR.: Carcinoma of the gall-bladder: the etiological role of gall stones, *Surgery*, 1940, vii, 657.
9. FINNEY, J. M. T., JR., and JOHNSON, M. L.: Primary carcinoma of the gall-bladder, *Ann. Surg.*, 1945, cxxi, 425.
- GREENLEE, D. P., HAMILTON, R. C., and FERRARO, F. P.: Primary carcinoma of the gall-bladder, *Arch. Surg.*, 1941, xlii, 598.
- KIRSHBAUM, J. D., and KOZALL, D. D.: Carcinoma of the gall-bladder and extrahepatic bile ducts, *Surg., Gynec. and Obst.*, 1941, lxxiii, 740.
- LAM, C. R.: The present status of carcinoma of the gall-bladder: a study of 34 clinical cases, *Ann. Surg.*, 1940, cxi, 403.
- MOHARDT, J. H.: Carcinoma of the gall-bladder: collective review, *Surg., Gynec. and Obst.*, 1939, lxi, 440.
10. HORNE, E. D.: Congenital hemolytic icterus, *Am. Jr. Surg.*, 1944, lxxv, 56.

## THE EARLY DEVELOPMENT OF SYPHILITIC AORTITIS \*

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THE clinical diagnosis of aortitis is usually made late in the course of syphilitic infection. Although the literature contains references to its early development, it is not generally appreciated that the condition may sometimes be found within a short time after the primary infection. In the case to be reported symptoms appeared 10 months after infection and death from heart failure occurred 22 months later.

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From the Medical Service, St. Luke's Hospital, Cleveland, Ohio.

## CASE REPORT

A colored male, aged 41 years, was seen in the Out-Patient Department October 25, 1944, complaining of dyspnea and orthopnea since August, 1943.

The past history is irrelevant except for the following important information: In 1928, Wassermann and Kahn reactions were negative in this hospital. On October 3, 1942, he received a pre-induction examination at his local draft board. No physical defects were noted and his serology was negative. Three weeks later, October 23, he was sent to the induction center where another physical examination was carried out. There was now a chancre present on the penis and the serology was positive. A careful survey of the heart including a teleroentgenogram revealed no evidence of cardiovascular disease. On account of the presence of infectious syphilis he was rejected for military service and was given heavy metal therapy by his private physician. This consisted of 16 injections of Mapharsen and 10 injections of bismuth with a lapse of several months during the course of arsenical therapy.

*Physical Examination.* The patient was in obvious respiratory embarrassment. The forceful pulsations of the carotid arteries were readily noticed. The pulse was of typical water-hammer character. The blood pressure was 170 mm. Hg systolic and 70 diastolic. The precordial activity was increased and the point of maximum intensity was in the anterior axillary line. The rhythm was regular. At the base of the heart both systolic and diastolic murmurs were heard. These were to-and-fro in character and of the type that we associate with aortic regurgitation. There were many râles in the chest and slight pitting edema, evidence of congestive failure.

The teleroentgenogram at this time showed an enlargement of the heart in all diameters, predominantly of the left ventricle. The transverse diameter measured 16.5 cm. as compared with the maximum normal of 12.6 cm. and represented an enlargement of more than 25 per cent above the expected normal figure. Mazzini and Wassermann reactions on the blood serum were strongly positive. It was our impression that this represented syphilitic aortitis with an unusually rapid onset. The cardiac status was placed in Class III.

*Subsequent Course.* The patient was confined to bed and after digitalization he was comfortable enough to leave the hospital on his nineteenth hospital day.

He was followed in the Cardiac and Venereal Disease clinics of this hospital. In December, 1944, weekly injections of bismuth subsalicylate were begun, a course of which was to precede the use of small doses of Mapharsen. He received, from December, 1944, to April, 1945, fourteen injections of bismuth subsalicylate 0.13 gm. Because of the progressively unfavorable course of the disease no Mapharsen was given. In spite of treatment and excellent coöperation on the part of the patient, cardiac failure increased in severity, necessitating many hospital admissions.

The seventh and last admission was on May 20, 1945, the patient having been discharged only six days before. He complained of abdominal pain, some diarrhea, and vomiting. Physical examination showed severe congestive heart failure and, for the first time, jaundice and an enlarged liver. The teleroentgenogram demonstrated a further increase in the size of the heart. The transverse diameter was 18 cm. The blood nonprotein nitrogen was 167 mg. per 100 c.c., and creatinine 3.5 mg. per 100 c.c. Serum icterus index was 50 units. Except for a slight trace of albumin the urine was not remarkable. For a while the failure lessened and concomitant with this there was a drop in the degree of nitrogen retention and icterus. On June 16, 1945, the nonprotein nitrogen was 41.8 mg. per 100 c.c., creatinine 1.2 mg. per 100 c.c., and the icterus index 17 units.

His condition then became worse and in spite of oxygen and other supportive measures he died on June 26, 1945.

*Autopsy Examination.* The important pathological findings were confined to the cardiovascular system. The heart weighed 640 gm. All chambers were dilated and hypertrophied, the left ventricular wall measuring 17 mm. in thickness. The aortic valve was normal but the circumference of the ring was increased to 9 cm. There were no changes in the mitral, tricuspid, or pulmonic valves. The coronary ostia were patent and the arteries were normal. The aorta showed a diffuse thickening extending to a level just above the celiac axis. The wall in this area was increased to 4 mm. in comparison to 1 mm. in thickness of the abdominal portion. The internal surface of the aorta was corrugated and pitted with many irregular, raised, pearly zones. The microscopic examination confirmed the gross diagnosis of syphilitic aortitis.

### CONCLUSION

In view of the systemic nature of syphilitic infection and the high incidence of aortitis found at autopsy, it is not surprising that signs of aortic involvement occasionally are seen early in the disease. The following reports from the literature will serve to illustrate what may be encountered. Brooks<sup>1</sup> reported rupture of the aorta just above the aortic leaflets in a patient with early secondary syphilis. Blackford and Smith<sup>2</sup> reported a case in which rupture of a gummatous aortic cusp occurred eight months after a positive darkfield primary. Reid<sup>3</sup> has studied a patient in whom aortitis developed three months after the initial infection. Sanford<sup>4</sup> reported the development of an aortic aneurysm in a 20 year old Negro, which resulted in death within two years after the primary infection.

In contrast to these extreme examples, the diagnosis in the average case is made much later. Cole and Usilton<sup>5</sup> found in their Coöperative Clinical Group study of 142 individuals in whom the onset of infection could be determined accurately, three patients in whom the condition had developed within five years. Most frequently the period was from 20 to 30 years after infection. Stokes<sup>6</sup> is of essentially the same opinion, indicating that 45 per cent of syphilitic aortitis is recognized in the second and 30 per cent in the third decade of the disease.

For the most part this is attributed to the fact that the disease lies dormant for many years but it may be that a thorough search for the condition is sometimes delayed until the infection has been present for a considerable period of time. The knowledge that syphilitic aortitis is occasionally encountered shortly after the initial infection may, in some cases, lead to its earlier recognition.

### BIBLIOGRAPHY

1. BROOKS, H.: The heart in syphilis, *Am. Jr. Med. Sci.*, 1913, cxlvi, 513.
2. BLACKFORD, L. M., and SMITH, C.: Syphilitic aortic insufficiency in negroes, *Am. Jr. Syph., Gonor. and Ven. Dis.*, 1938, xxii, 146.
3. REID, W.: Specific aortitis, *Boston Med. and Surg. Jr.*, 1920, clxxxiii, 67 and 105.
4. SANFORD, S. P.: An unusual case of aortic aneurysm, *Ann. Int. Med.*, 1945, xxii, 599.
5. COLE, H. N., and USILTON, LIDD J.: Coöperative clinical studies in the treatment of syphilis: cardiovascular syphilis, *Arch. Int. Med.*, 1936, lvii, 910.
6. STOKES, J. H., BEERMAN, H., and INGRAHAM, N. R., JR.: *Modern clinical syphilology*, 1945, 3rd ed., W. B. Saunders Co., Philadelphia, p. 897.

## ERUPTIVE FEVER WITH STOMATITIS AND OPHTHALMIA (STEVENS-JOHNSON)\*

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IN their discussion of the erythema multiforme group of dermatoses, Sutton and Sutton<sup>1</sup> listed a subvariety: eruptive fever with stomatitis and ophthalmia, *ectodermose érosive pluriorificielle*, or dermatostomatitis. This syndrome has also been called erythema multiforme of the Stevens-Johnson variety; for it was Stevens and Johnson<sup>2</sup> who in the American literature first proposed the designation of this group as an entity apart from *erythema exudativum multiforme* (Hebra). These authors introduced the disease as "a new eruptive fever associated with stomatitis and ophthalmia." However, similar cases have been described previously by Rendu<sup>3</sup> and Fiessinger and Rendu<sup>4</sup> as "ectodermoses érosives pluriorificielles."

Within two years there were admitted to the general medical service, two patients suffering from disorders that fit the descriptions of Stevens-Johnson's disease. The following are the essential data for each case.

### CASE REPORTS

*Case 1.* A 19 year old white male was admitted to the medical service on February 21, 1944, with the chief complaints of cough and sore throat. For several days the patient suffered from a "cold." Four days prior to admission he began to have chills, fever, and sweats. In addition, he developed a harassing dry cough and sore throat. Aside from aspirin and cough syrup containing codeine, the patient had taken no other medication.

In the past, he had suffered from eczema on his face, neck, and in the antecubital fossae, recurring in the late winter and early spring months. In addition, one sister suffered from eczema.

The physical examination revealed a moderately ill white male, dull and apathetic. Temperature, pulse, and respirations were 104° F., 120, and 26 respectively. His eyes exhibited injection of the conjunctivae and the sclerae with some purulent discharge. His nose was congested, and his throat was intensely inflamed. Examination of the chest revealed a few scattered râles at both bases, but other abnormal signs were lacking. The skin felt hot and dry, and in the antecubital fossae there was evidence of a healed atopic eczema. It was the impression that the patient was suffering from an atypical pneumonia.

The laboratory findings were as follows: Blood count: hemoglobin 14 gm.; white blood cell count 11,500, neutrophils 76 per cent; lymphocytes 22 per cent; eosinophils 1 per cent; and monocytes 1 per cent. Examination of the neutrophils revealed a shift to the left and the presence of marked toxic granulations.

Urinalysis: normal. Chest roentgenogram: normal. Kahn test: negative. Heterophile antibody test: negative. Sedimentation rate: 65 mm. per hour. Throat smear: a few Vincent's organisms and the usual bacterial flora. Smear and culture from the secretion in the eyes: many pus cells present, but no organisms present on smear and culture.

Twenty-four hours later, mouth lesions began to appear. The mucous membranes of the mouth, tongue, and throat were covered with several patches of foul smelling,

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From the Medical Service of the AAF Station Hospital, Seymour Johnson Field, N. C.

dirty yellowish matter. In addition, there was a thick purulent post-nasal discharge. The picture was not unlike an extensive Vincent's infection. At the same time, a painful red papule appeared on the anterior surface of the glans penis. There were no skin lesions present.

Treatment consisted of sulfadiazine orally and sulfathiazole ointment to the eyes. Supportive therapy, including vitamin administration, was instituted. Improvement was gradual. The temperature returned to normal by lysis on the ninth hospital day, and the patient was asymptomatic by the twenty-second day.

Sensitivity (scratch) tests were performed after the patient had fully recovered. He was found to be strongly allergic to dusts, horse dander, chicken feathers, goose feathers, and sheep dander.

*Comment:* This was a case of erythema multiforme involving chiefly the mucosa of the mouth, throat, eyes, and skin of the glans penis. The syndrome had as the onset an apparent upper respiratory infection. The allergic background as evidenced by an old eczema and positive skin tests may have played a rôle as an etiologic factor; but, on the other hand, at no time during the disease did the allergy flare up.

*Case 2.* A 20 year old white male was admitted on December 25, 1945, complaining of burning and discharge from his eyes, soreness in the nose and mouth, and a discharge from the penis. Several days prior to the onset, he had a cold consisting of a slight nasal discharge. On December 20, he noted burning and crusting about his eyes. His gums became tender on the next day and bled on slight trauma. The penile discharge and soreness began December 22. On this date he took three tablets of "Ex-Lax."

The past history and family background were non-contributory. The patient's last sex exposure was alleged to have occurred six weeks prior to admission. Previous venereal disease was denied.

The physical examination revealed a moderately ill white male. Temperature, pulse, and respirations were 100.6° F., 80, and 20. The conjunctivae were injected and a mucopurulent secretion was present. His face appeared flushed and slightly edematous. The nasal mucous membrane was covered with small crusted ulcerations. Similar large necrotic plaques were present on the gums, buccal mucosa, hard and soft palates. The cervical nodes were somewhat enlarged. Except for the genitalia, the remainder of the physical examination was negative. On the tip of the glans there was an ulceration. The glans penis was reddened and covered with a dirty grayish exudate. Thick purulent material could be expressed from the meatus.

Laboratory findings on admission were: Complete blood count: hemoglobin 15.8 grams; white blood cell count 7,100 with 67 per cent neutrophils, 27 per cent lymphocytes, 5 monocytes, and 1 per cent eosinophiles. Kahn test: negative. Urethral smear: many pus cells with Gram negative intra- and extracellular diplococci. Cultures were positive for gonococci. Conjunctival smear; many pus cells present with an occasional cell containing Gram negative diplococci. The appearance was that of a Neisserian infection, but could not be identified with certainty, for cultures revealed no growth. Smear of the mouth and throat: mixed bacterial flora and Vincent's organisms. Blood cultures were not taken.

Treatment with penicillin was instituted in dosage of 20,000 units every three hours by the intramuscular route. Five per cent sulfathiazole ointment was used in the eyes. Attention was also given to oral hygiene. Vitamins were administered in large doses. Within 24 hours the patient was afebrile. The urethral discharge had disappeared, and the secretion from the eyes lost its purulent character. Microscopic examination of the urethral smear revealed the disappearance of the gonococci and a

lessening of the number of pus cells. By the fifth hospital day the balanitis had almost cleared; the conjunctivitis was receding rapidly; but the lesions in the mouth and throat remained unchanged. In addition, ulcers were appearing on the margins of the tongue. On the anterior aspects of the legs and extensor surfaces of the arms there were small reddish maculopapules averaging one centimeter in diameter. Some were hemorrhagic, whereas others developed small vesicles in the center. On the seventh hospital day his mouth began to heal, the balanitis and the conjunctivitis had disappeared, and no new skin lesions had appeared. By January 8, twenty days after the onset of the conjunctival discharge, the patient was asymptomatic. Penicillin, given for the first 11 days, totalled 1,760,000 units.

Comment: This was a mild case of dermatostomatitis. Again, prior to the onset, the patient had a mild upper respiratory infection. The ingestion of the laxative containing phenolphthalein occurred after the onset of the disease. The possibility was suggested that the picture was one of a widespread gonococcal infection as described by Keil.<sup>5</sup> However, the type of mouth lesions were not those seen in Neisserian infections. Gonococcal stomatitis has been reported in the newborn.<sup>1</sup> Probably the patient harbored the organisms, which in turn were activated by the erythema multiforme. This is comparable to those cases wherein secondary infections occur with pyogenic organisms.

### DISCUSSION

Although they are included in the category of erythema multiforme, cases of dermatostomatitis exhibit distinctive clinical courses. Cases have been reported by Stevens and Johnson,<sup>2</sup> Ginandes,<sup>6</sup> Klauder,<sup>7</sup> Ageloff,<sup>8</sup> Ellis,<sup>9</sup> Murphy,<sup>10</sup> and Kove.<sup>11</sup> The disease usually attacks children and young adult males. The onset is rather acute, with the appearance of a conjunctivitis and bullous lesions on the mucosa of the mouth and nose. Often vesicular or ulcerative lesions appear on the penis. The anus may likewise be involved. Constitutional symptoms are frequently present, are severe, and associated with high fever and moderate to marked toxicity. The mouth becomes filled with ulcerations covered with dirty necrotic exudate. A few days after onset cutaneous lesions may appear. They range from maculo-papules to bullae. If complications are averted, healing begins in about one week with remission in the constitutional symptoms and is complete in from three to six weeks. However, secondary infections with pyogenic bacteria often occur, affecting chiefly the eyes, producing a purulent conjunctivitis and corneal involvement. A panophthalmitis may subsequently lead to blindness.<sup>2, 6</sup> During the course of the disease laboratory examinations of blood and urine are not characteristic.

The diagnosis is often confused with various types of stomatitis and especially with that due to Vincent's organisms. Conjunctivitis from different causes, venereal diseases, reactions of sensitivity to various drugs, and some of the infectious exanthemata enter into the differential diagnosis. In fact, the patient may first seek aid from a dentist, ophthalmologist, or urologist. However, the course of the disease and the definite association of conjunctivitis and stomatitis, with cutaneous and genital lesions, are very suggestive.

Death may occur as a result of secondary sepsis or toxemia with extensive involvement. From cases designated as erythema exudativum multiforme with stomatitis and ophthalmia the pathology has previously been reported by Edgar and Syverton<sup>12</sup> and Fletcher and Harris.<sup>13</sup>

The treatment of the Stevens-Johnson syndrome is non-specific. Scrupulous oral hygiene is necessary. The eyes should be irrigated frequently if secretion is present. Cutaneous lesions may be treated by local applications when necessary. Because of the soreness of the mouth, feeding is a problem. The patient should be served a liquid or soft diet of high caloric content. Citrus fruits and vinegar are usually too irritating. Supplementary vitamin intake is necessary. Parenteral therapy may be required to combat toxicity and supplement the fluid and nutrient intake.

Secondary infection may lead to a prolonged convalescence, total disability, or a fatal outcome. With the relatively new therapeutic weapons, complications can be averted or treated if they occur. The first case was given sulfadiazine by mouth and sulfathiazole ointment on the eyes. In the second case, penicillin was administered by the parenteral route and sulfathiazole ointment locally for the eyes. Although this patient was moderately ill, the clearance of the secondary infection was prompt. Penicillin has the further advantage of eliminating the Vincent's organisms, which may aggravate the stomatitis already present. It is doubtful that penicillin is specific for dermatostomatitis; for in the patient treated with the drug, the skin and mouth lesions continued to appear and ran their usual courses.

The etiology of this symptom-complex remains unknown. It is doubtful whether any one etiologic factor can be designated as the primary agent in any given case. In each of the patients reported in the article the onset was preceded by an upper respiratory infection; drugs could not be implicated. A similar onset has been cited by Klauder,<sup>7</sup> Rosenberg and Rosenberg,<sup>14</sup> and Edgar and Syverton.<sup>13</sup> Drugs acted as predisposing factors in other patients. Ellis<sup>9</sup> reported one case following the use of phenytoin sodium, and Fletcher and Harris<sup>13</sup> presented two resulting from ingestion of sulfadiazine and Fowler's solution. The resemblance to foot and mouth disease in humans has been emphasized by Klauder,<sup>7</sup> but this could not be proved in the laboratory. A case following the onset of mumps was reported by Kove.<sup>11</sup> Inoculations of various laboratory animals with fluid from the cutaneous blebs failed to produce any positive findings.<sup>12, 15</sup> The possibility of a state of hypersensitivity is suggested by the reactions of the skin and mucous membranes to either drug ingestions or infection.

There exists disagreement as to whether Stevens-Johnson's disease is a clinical entity. This fact further confuses the search for the causative factor; for the same disease may be reported in the literature as Stevens-Johnson's disease or as a variant of *erythema exudativum multiforme*. Stevens and Johnson<sup>2</sup> and Ginandes<sup>6</sup> presented arguments in favor of the syndrome as a separate disease. On the other hand, Klauder<sup>7</sup> and Keil<sup>16</sup> take the opposite view. It appears from the findings of various predisposing factors that eruptive fever with stomatitis and ophthalmia should be listed as a subgroup of *erythema multiforme*. As Keil<sup>16</sup> points out, mucous membrane lesions actually occur in many patients with *erythema multiforme*, contrary to opinions of earlier authors. Further, cases have been reported as Vincent's infection with *erythema multiforme*,<sup>17, 18</sup> conjunctivitis with cutaneous concomitants,<sup>15, 19</sup> or mucosal lesions without dermatitis.<sup>20</sup> The conclusion is that Stevens-Johnson's disease is a variant of *erythema exudativum multiforme*. However, in view of the clinical similarity of various cases, the retention of the name offers the physician considerable information as to the prognosis and therapeutic approach.



## SUMMARY

Two cases of erythema multiforme of the Stevens-Johnson variety have been reported. In one patient there appeared to be secondary invasion by gonococci from possibly a latent urethritis. Penicillin treatment over a period of several days checked the secondary infection without altering the course of the dermatostomatitis.

A brief discussion of the etiologic factors is presented. No single factor could be pointed out as the cause of Stevens-Johnson's disease.

Doubt is registered as to whether the disease is in itself a clinical entity.

## BIBLIOGRAPHY

1. SUTTON, R. L., and SUTTON, R. L., JR.: Diseases of the skin, 10th Ed., 1939, C. V. Mosby Co., St. Louis, p. 146 and 1496.
2. STEVENS, A. M., and JOHNSON, E. C.: A new eruptive fever associated with stomatitis and ophthalmia, *Am. Jr. Dis. Child.*, 1922, xxiv, 526.
3. RENDU, R.: cited by Sutton and Sutton.
4. FIESSINGER, N., and RENDU, R.: cited by Fletcher and Harris.
5. KEIL, H.: A type of gonococcal bacteremia with characteristic hemorrhagic vesiculopustular and bullous skin lesions, *Quart. Jr. Med.*, 1933, vii, 1.
6. GINANDES, G. J.: Eruptive fever with stomatitis and ophthalmia—Atypical erythema exudativum multiforme (Stevens-Johnson), *Am. Jr. Dis. Child.*, 1935, xlix, 1148.
7. KLAUDER, J. V.: Ectodermosis erosiva pluriorificialis: Its resemblance to the human form of foot and mouth disease and its relation to erythema exudativum multiforme, *Arch. Dermat. and Syph.*, 1937, xxxvi, 1067.
8. AGELOFF, H.: Erythema multiforme bullosum with involvement of mucous membranes of eyes and mouth (Stevens-Johnson disease), *New England Jr. Med.*, 1940, ccxxiii, 217.
9. ELLIS, F. A.: Reactions to nirvanol, phenytoin sodium, and phenobarbital, *South. Med. Jr.*, 1943, xxxvi, 575.
10. MURPHY, R. C., JR.: Eruptive fever involving mouth and eyes (Stevens-Johnson disease), *New England Jr. Med.*, 1944, ccxxx, 69.
11. KOVE, S.: Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis), *Am. Jr. Med. Sci.*, 1945, ccx, 611.
12. EDGAR, K. J., and SYVERTON, J. T.: Erythema exudativum multiforme with ophthalmia and stomatitis: Report of two cases in children with certain observations on histopathology and animal inoculation, *Jr. Pediat.*, 1938, xii, 151.
13. FLETCHER, M. W. C., and HARRIS, R. C.: Erythema exudativum multiforme (Hebra)—bullous type, *Jr. Pediat.*, 1945, xxvii, 465.
14. ROSENBERG, L., and ROSENBERG, J.: Erythema exudativum multiforme (Hebra) with conjunctivitis and stomatitis, *Arch. Dermat. and Syph.*, 1940, xli, 1066.
15. KOKE, M. P.: Conjunctivitis in erythema exudativum multiforme: Report of three cases, *Arch. Ophth.*, 1941, xxv, 78.
16. KEIL, H.: Erythema multiforme exudativum (Hebra), a clinical entity associated with systemic features, *Ann. Int. Med.*, 1940, xiv, 449.
17. CASKEY, C. R.: Vincent's angina associated with unusual skin manifestations, *Urol. and Cut. Rev.*, 1932, xxxvi, 370.
18. CHICK, F. E., and WITZBERGER, C. M.: Erythema multiforme exudativum accompanying oral Vincent's infection, *Am. Jr. Dis. Child.*, 1938, lv, 573.
19. BAILEY, J. H.: Lesions of the cornea and conjunctivitis in erythema exudativum multiforme (Hebra), *Arch. Ophth.*, 1931, vi, 362.
20. BUTLER, J.: Erythema multiforme confined to the mucous membrane, *Arch. Dermat. and Syph.*, 1922, vi, 1.

## EDITORIAL

### *A PRELIMINARY NOTE ON AN INTERESTING EXPERIMENT*

ON April 15, 1934, as an aid to the promotion of clinical research in this country, the Board of Regents established the "Research Fellowship of the American College of Physicians." This fellowship, on recommendation of the Committee on Fellowships and Awards, was given each year from 1934 to 1943—when war interrupted the program—to a varying number of suitably promising candidates, no single one ever holding it for more than a period of 12 months.

The Committee on Fellowships and Awards, first called the Committee on the John Phillips Memorial Prize, was established in 1929 as a committee of five with its membership appointed by the President. The President was given free hand in regard to the composition of the committee except that not less than two or more than three of its members could be re-appointed in any year. This device was evidently employed to prevent stagnation within the committee and to ensure a continued influx of new ideas.

The Committee, too, was given free hand; one of its important aims after 1934 was to develop the fellowship as a project which might come to play an increasingly distinctive part in the work of the College. With this idea in mind, while the Board of Regents made the appointments technically, the Committee was authorized to nominate the successful candidate or candidates each year, after combing them from a carefully censored list obtained through communicating with the professors of medicine and pediatrics in the country, with the officers and regents of the College, and with the National Research Council. The last agency was inserted so that nominations might be obtained from this source in case the professors of medicine and pediatrics and the officers and regents were unable to suggest any young men or women of sufficient promise. And finally, in order to systematize its work, the Committee adopted an application form of the general type developed by the National Research Council; in this way the necessary biographical data and attainments of each candidate were recorded in a manner that was uniform and of proved usefulness.

Up to the beginning of the war, 16 fellows had been appointed in this fashion. While their number is small and the possible years of follow-up on their careers are few, yet it has seemed worth while to attempt to evaluate their work. One might argue that if, on the whole, the holders of such fellowships had by now succeeded in accomplishing demonstrably satisfactory results in research, the continuance of such appointments was justified; if not, the funds of the College allocated for their maintenance might, perhaps, be used to better advantage for some other purpose.

The policy of the Committee during the period under consideration was relatively fixed: all Research Fellows were young and were men of reliable

character; they were graduates of different medical schools; and they were chosen a few years after completion of their medical course because already they had exhibited a talent and liking for research or at least had displayed more than normal curiosity as interns or residents in attempting to solve the riddles of clinical medicine. Also, they were chosen, in part, because they needed the financial aid from the stipend attached to the fellowship.

TABLE I

The Age of the Research Fellows When They Were Appointed and Their Medical Schools

Name	Medical School	Year of Graduation	Year of Appointment as Fellow	Age at Time of Appointment
W. R. A.	Ohio State	1938	1941	31
W. W. B.	Harvard	1935	1940	30
L. D.	Harvard	1936	1940	30
A. M. H.	Johns Hopkins	1934	1937	26
C. G. H.	Wisconsin	1940	1942	29
J. H.	California	1939	1942	32
F. K.	Harvard	1931	1934	28
M. J. L.	Rochester	1934	1935	24
H. M.	So. California	1938	1939	26
M. P.	California	1933	1936	28
R. W. R.	Northwestern	1938	1941	33
H. S.	Oklahoma	1936	1940	29
J. R. S.	Washington Univ.	1934	1938	29
M. T.	Yale	1936	1940	31
R. H. W.	Johns Hopkins	1934	1939	30
R. W. W.	Harvard	1933	1937	31

Of the 16 men involved in this study, four were Harvard graduates, two were from Johns Hopkins, two were from the University of California, and the rest were from scattered schools. That half were graduates of only three schools appears to be fortuitous. As a composite group they averaged 29 years in age when they received the appointment and were about three years out of medical school.

By tradition, the Committee has required information as to where each prospective fellow wished to work during the year of his appointment and on what kind of problem, as well as reassurance that were he to receive a fellowship he would be welcome to work in the clinic or laboratory of his choice. Three of the fellows finally selected planned to work in England, one in Cairo under Professor Anrep, and one in Buenos Aires under Professor Houssay. The rest, except one, had chosen American University clinics, and of these, Yale was the most popular since three men desired to spend a year at New Haven. The lone exception hoped to improve his knowledge in chemistry by working at the Rockefeller Institute Hospital under Dr. Van Slyke.

This gives a cursory description of what the Fellows were like and their aspirations.

Two criteria were adopted to measure what the Research Fellows have accomplished: the first is bibliographic and the second academic. Their publications, as listed in the Quarterly Cumulative Index Medicus, were tabulated. Since, at the time of preparing this report, no volume of the Index after June 1946 was available, only publications were included which had appeared in 1945 or previously. As judged in this way, these 16 young men, following their introduction to clinical research under the College's auspices, have already contributed more than 200 articles to medical literature. The manner in which this literature has grown is one of its most gratifying features.

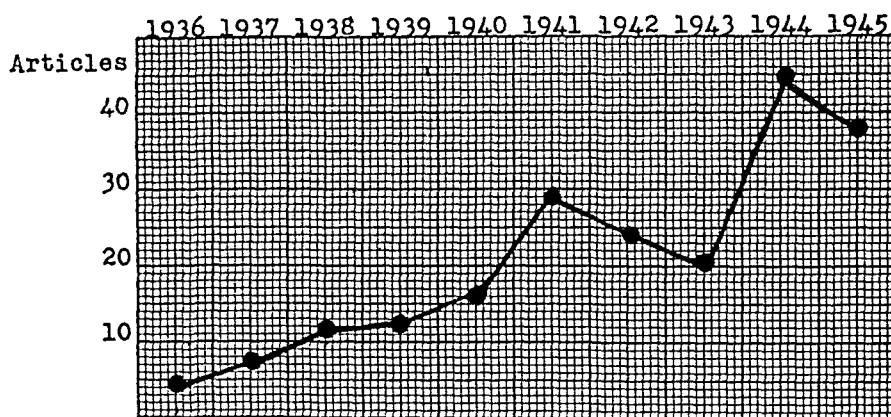


FIG. 1. The printed record in medical periodicals of the Research Fellows.

There has been a rising tide of readable papers flowing from their pens, interrupted during 1942 and 1943 by the war but regaining momentum in 1944 and 1945. This record is impressive. No evidence of mental sterility or laziness has developed amongst the Fellows; rather, once having been exposed to the satisfaction of clinical investigation they have appeared to react as did Dr. Oliver Wendell Holmes when he first came in mental contact with pride of authorship and, like him, they have continued to be productive.

They have written serious papers, as judged by their vehicles of publication. For example, 17 of their articles have been printed in the *Annals of Internal Medicine*, 17 in the *Journal of Clinical Investigation*, 13 in the *American Heart Journal*, 11 in the *Journal of Physiology*, and almost all of the rest in periodicals of equal respectability or gravity. Occasional—and very readable—reports have been prepared for the benefit of men in general practice and have appeared in various state medical journals. There has been almost no literary padding.

In looking over the titles listed, two striking facts become apparent. The first is the diversity of interests which the Fellows have developed. Most of them have approached clinical research through the disciplines of physiology, chemistry, bacteriology or pharmacology rather than through the more

ancient ones of anatomy or pathology; they have probed almost every corner of medicine with new instruments in an effort to lay bare the fundamentals of disease.

The second reveals the obvious need for team-play in modern clinical research. The majority of investigations which have been described were completed by several men working together rather than by any single individual working alone. Thus it is probable that our Research Fellows have exerted a perceptible influence on their associates, stimulating colleagues to work with them and helping to transfer new ideas and methods from one part of the world to another. Mainly, however, their publications reveal the astonishing complexity of modern clinical research; teams comprising physicists, chemists, surgeons, internists, radiologists, pathologists and bacteriologists are now often needed to pry open even a narrow doorway to new medical knowledge.

As judged by academic standards, the Fellows have made an equally impressive record. The most venerable has scarcely passed his fortieth birthday and yet among the group there are now one professor of medicine, one associate professor, and six assistant professors serving on medical faculties; almost all the rest occupy positions weighted with research or teaching responsibilities; so far, the lure of private practice has proved a poor competitor against scientific ambition.

Certainly, the first crop of Research Fellows has helped to promote clinical research in this country in a way that is gratifying and which has added to the prestige of the College. The question arises as to whether the second

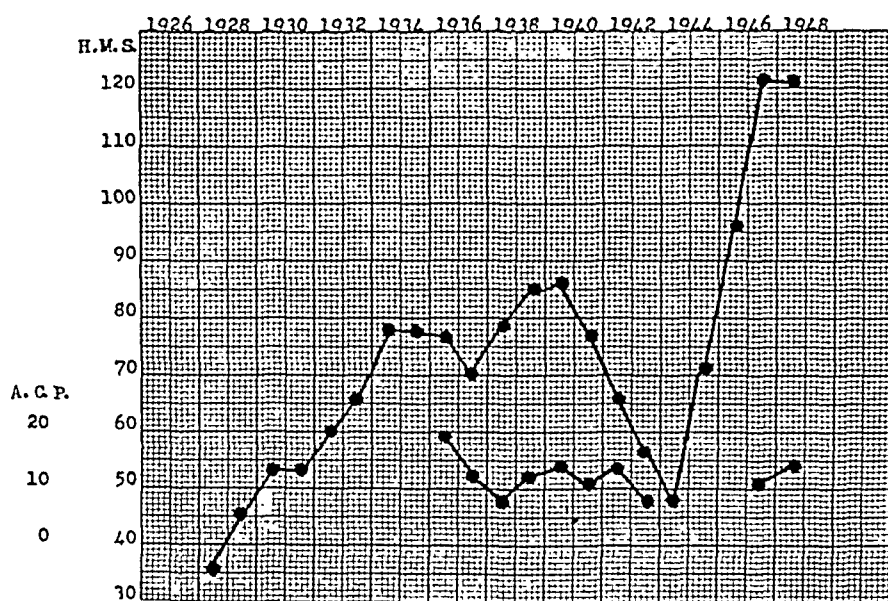


FIG. 2. The apparent growth in research fellowship opportunities. The upper line represents the number of Research Fellows as listed in the Catalogue of the Harvard Medical School year by year. The lower line represents the number of candidates applying for Research Fellowships offered by the College.

crop—which was planted in 1946—can continue to yield so luxuriant a harvest.

Conditions now are far different than they were in 1934; vast sums of money have been set aside by various foundations or institutions to encourage research fellowships along principles followed by the College, and the number obtainable has increased by leaps and bounds. The accompanying graph was prepared to illustrate what has occurred.

The Harvard Medical School was selected as an example because its catalogues happened to be easily available. Presumably, the experience of Harvard is not unique; about 20 years ago funds for research began to become available from a variety of sources and in increasing amounts, so that the number of individuals who benefited by them as research fellows grew rapidly. When war broke out, Harvard deliberately set aside research fellowship funds to be used later; it was impossible to find enough properly trained young doctors to expend them at the time and it seemed only fair to hold them in reserve for the benefit of returning veterans who might use them to great advantage later. Thus, the large number of Harvard research fellows in 1946 and 1947 is, in a sense, an artefact. Yet the trend of the curve is unmistakable.

The number of applicants for the College's research fellowships, in contrast, has remained almost constant each year. The correct interpretation of what this signifies is problematical. Does it mean that those who nominate candidates for the Fellowships are extremely critical and, as a result, that the College selects from only the topmost level of all young doctors who think they wish to pursue a research career? Or does it mean that so many research fellowships are now available as to dilute the value of those offered by the College, making them more commonplace and of no great distinction?

The correct answer to these questions, clearly, at present, is uncertain. Yet one disconcerting fact has appeared from this study. Of 16 Research Fellows appointed by the College, only two have joined it and only one has become an Associate. The remaining 13 have appeared to show no interest whatsoever in the College or what it stands for. This record is all the more disconcerting because, under the old by-laws, nearly all of this group were eligible to become associates when they accepted the fellowship and by now six of them have been certified by the American Board of Internal Medicine so that election to the College should not be too difficult. On the whole, either indifference to the College or ignorance of its work must be the explanation. In future, the College should cultivate the loyalty and interest of its research fellows more actively than it has in the past.

The College, through its Research Fellowships, has conducted an interesting experiment in medical education which already has yielded interesting results. The continuance of the experiment for a longer period of time seems justified. The Fellows, however, must always be chosen with particular care, and especially so in times when fellowship funds are prevalent.

Those selected must appear to offer promise of achieving national prominence in medicine from the impetus they obtain at the beginning of their careers as Research Fellows of the American College of Physicians. If other than young people of rare ability and earnestness of purpose receive it, the Fellowship will degenerate and its maintenance will fail to promote and advance clinical research in any distinctive fashion of which the College can be proud.

REGINALD FITZ, M.D., F.A.C.P.\*

\* Chairman, Committee on Fellowships and Awards, 1947.

## REVIEWS

*Allergy in Theory and Practice.* By ROBERT A. COOKE, M.D., ScD., F.A.C.P., Attending Physician and Director of the Department of Allergy, The Roosevelt Hospital, New York City, and Associates. 572 pages; 16 × 24 cm. 1947. W. B. Saunders Company, Philadelphia, Pennsylvania. Price, \$8.00.

This volume represents a series of articles by Dr. Cooke and thirteen collaborators based upon the less formal lectures given in courses on allergy arranged in coöperation with the American College of Physicians. The magnitude of Dr. Cooke's contribution is evidenced by his being responsible for approximately 241 pages of the text.

The volume was designed to orient physicians to allergy rather than to offer an exhaustive text on the one hand or, to present the material in such simple language that the layman or the totally uninformed physician could understand the subject. The attitude of the authors is that a reasonable well educated physician can understand a technical subject if it is clearly presented without cheapening the presentation with futile attempts at over-simplification. This volume places allergy in the general field of medicine with gratifying precision. It shows its relationship to immunological processes and, also clinical medicine.

As his dominant rôle in this phase of the subject would suggest, Dr. Cooke's contribution on the basic processes is excellent, particularly as they concern immunologic mechanisms. The same is true of Heidelberger's section on the immuno-chemistry of antigens and antibodies.

The other portions of the book on the clinical phases of allergy are entirely adequate if the purpose of the book is kept in mind, namely, the introduction of allergy to physicians rather than a detailed text covering every aspect of the subject. It should be particularly valuable as a source of teaching material for undergraduate medical students.

The reviewer heartily recommends this book and is of the opinion that, in a distinguished fashion, it has accomplished the purpose for which it was designed.

H. M. B.

*The Acute Infectious Fevers, An Introduction for Students and Practitioners.* By ALEXANDER JOE, D.S.C., M.D.(Ed.), F.R.C.P.(Ed.), D.P.H., D.T.M. & H., Medical Superintendent, City Hospital, Edinburgh, Lecturer on Infectious Diseases to the University of Edinburgh, Formerly Medical Superintendent, North-Western Hospital, London. 276 pages, 13.5 × 22.5 cm. 1947. The Blakiston Co., Philadelphia, Pa. Price, \$4.50.

The author has provided the answers to many practical questions confronting practitioners who treat the common acute infectious fevers. Logically presented are the pathology, etiology, transmission, infectivity, incubation and quarantine period, clinical features, complications, diagnoses, prognoses, prophylaxis and treatment of each individual entity. Of great value are the pertinent new researches, laboratory procedures and therapeutic weapons needed for the modern handling of infectious processes. Abundantly and well illustrated, clearly written, this book will serve the student and general practitioner. The sections on scarlet fever, diphtheria and cerebral spinal fever are outstanding, but the author's conception of all the fevers is thoroughly modern.

T. E. W.

*Advances in Pediatrics (Volume II).* Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School,



Boston; L. EMMETT HOLT, JR., New York University, College of Medicine, New York; A. ASHLEY WEECH, Univ. of Cincinnati College of Med., Cincinnati. 409 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, \$6.75.

After an absence of five years, the second volume of the series, "Advances in Pediatrics," makes its appearance and a welcome one it is.

The book follows closely the pattern set down by the editor of the initial volume. The book consists of an excellent collection of comprehensive personalized monographs by outstanding authorities on selected subjects of pediatric interest. The pediatric menu is as follows: etiology of congenital malformations, acute infectious lymphocytosis, rôle of fluorine in prevention and treatment of dental caries, the treatment of purulent meningitides, chemotherapy, atypical pneumonia, endocrine and other factors influencing the growth of children, virus diarrhea, prematurity, genesis of physiologic hyperbilirubinemia and prevention of recurrences of rheumatic fever. Each of the sections is accompanied by an extensive bibliography to recent literature.

The volume is larger by one hundred pages than its predecessor, contains eighty well selected illustrations and numerous tables.

Several chapters were of particular interest to this reviewer. The section on prematurity puts emphasis on the "physiologic handicaps" and metabolism of the premature infant. This is discussed in a concise, complete manner. The use of low fat feedings for prematures in the form of skimmed milk preparations is advocated, based on the author's original work in association with one of the editors (Gordon and Levine).

Stimulating reading is provided by the paper on etiology of congenital malformations, which directs attention toward the line of teratologic investigation.

The aims of the editors are well carried out in the volume. It is highly recommended to all students of pediatrics who desire to keep abreast of present developments.

A. H. F.

*The X-Ray Treatment of Accessible Cancer.* By W. WALDRON SMITHERS, M.D., D.M.R. 147 pages; 19 × 27.5 cm. The Williams & Wilkins Co., Baltimore. 1946. Price, \$8.50.

The book deals with cancer in accessible areas or in areas made accessible by surgery. The material is very well illustrated (many of the photographs being in color) and numerous tables summarize the results. The author stresses the importance of adapting the technic of treatment to the clinical condition met with, in order that radiation therapy may be placed on a more rational basis.

A method of gauging the response of the tumor to radiation is described. Serial biopsies are taken and in the sections "cells in the growing portions of the tumor are counted and classified into: (1) mitotic; (2) degenerating; (3) differentiating and (4) resting cells"—the proportions of each are then plotted in a graph against time. From this the radiologist can determine if treatment is sufficient, inadequate or ineffectual. If ineffectual, surgery can be resorted to before the disease has time to get out of control.

The author stresses the need for very complete records, as to full description of extent of the disease (including measurements of primary), details of treatment and adequate follow-up; for without them our own results cannot be evaluated nor can results of various clinics be compared with any degree of accuracy.

This book will prove of value as a reference to practicing radiologists and especially in those clinics which train men.

A. G. S.

## BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*American Illustrated Medical Dictionary (The)* (21st Edition). By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lt. Col., M.R.C., U. S. Army, Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association, etc. 1660 pages; 24 × 16 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$8.00 without thumb index; \$8.50 with thumb index.

*Calcific Disease of the Aortic Valve*. By HOWARD T. KARSNER, M.D., and SIMON KOLETSKY, M.D., Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland. 111 pages; 23.5 × 15.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$5.00.

*Developmental Diagnosis: Normal and Abnormal Child Development—Clinical Methods and Pediatric Applications* (2nd Edition, Revised and Enlarged). By ARNOLD GESELL, M.D., and CATHERINE S. AMATRUDA, M.D. 496 pages; 24 × 16 cm. 1947. Paul B. Hoeber, Incorporated, Medical Book Department of Harper & Brothers, New York. Price, \$7.50.

*Dictionary of the Physiology of Man* (in Italian). By GAETANO MARTINO, Professor of Human Physiology at the University of Messina, Sicily. 305 pages; 24.5 × 18 cm. 1945. Azienda Poligrafica Editoriale, Catania, Italy. Price, 800 lire.

*Erkrankungen des Uropoetischen Systems und der Prostata durch Störung der Blutströmung* (in German). By PROFESSOR KARL HUTTER, Facharzt für Urologie, Wiener Beiträge zur Urologie, Herausgegeben von Prof. Dr. Richard Uebelhor: Band I. 200 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, \$4.00.

*Internal Medicine in General Practice* (2nd Edition). By ROBERT PRATT McCOMBS, B.S., M.D., F.A.C.P., Assistant Professor of Medicine and Director of Postgraduate Teaching, Tufts College Medical School, etc. 741 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$8.00.

*An Introduction to Biochemistry* (3d Edition). By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., Fellow of Trinity College and Professor of Biochemistry, University of Dublin, etc. 569 pages; 22.5 × 14.5 cm. 1947. Grune & Stratton, Inc., New York. Price, \$6.00.

*Lessons of Medical Clinic, Vol. I* (in Italian). By LUIGI CONDORELLI, University of Catania. 187 pages; 21 × 15 cm. 1947. Azienda Poligrafica Editoriale, Catania. Price, 655 lire.

*Morphologic Hematology*, Special Issue No. 1 of BLOOD, The Journal of Hematology. By WILLIAM DAMESHEK, M.D., Editor-in-Chief. 200 pages; 26 × 18 cm. 1947. Grune & Stratton, Inc., New York. Price, \$4.75.

*Ocular Therapeutics*. By WILLIAM J. HARRISON, Phar.D., M.D., F.A.C.S., Associate Professor in Ophthalmology, Jefferson Medical College, etc. 112 pages; 20 × 14.5 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$3.50.

*Pharmacology, Therapeutics and Prescription Writing: For Students and Practitioners* (5th Edition). By WALTER ARTHUR BASTEDO, Ph.G.; Ph.M/. (Hon.), M.D., ScD. (Hon.), F.A.C.P., Consulting Physician, St. Luke's Hospital, New York, etc. 840 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$8.50.

*Physiopathology of the Venous Circulation* (in Italian). By LUIGI CONDORELLI, Director of Medical Clinic at the University of Catania, Sicily. 336 pages; 25 × 17.5 cm. 1947. A.P.E. Degli; U. & G. Pagnano, Catania. Price, 1200 lire. (Publishers have provided for translation into English.)

*Rypin's Medical Licensure Examinations: Topical Summaries, Questions, and Answers* (6th Edition). Under the Editorial Direction of WALTER L. BIERRING, M.D., F.A.C.P., M.R.C.P., Edin. (Hon.), Former Member, National Board of Medical Examiners, etc. 690 pages; 24 × 16 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$6.00.

*A Textbook of Clinical Neurology, With an Introduction to the History of Neurology* (6th Edition). By ISRAEL S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University, New York, etc. 829 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$8.50.

*Time for Circle and Districtal Speed of Current in Physiopathology and in Clinic* (in Italian). By A. FRANCAVIGLIA and A. TURCHIETTI, with a preface by PROF. L. CONDORELLI. 254 pages; 24.5 × 17 cm. 1946. Azionda Poligrafica Editoriale, Catania. Price, 680 lire.

*Trichomonas Vaginalis and Trichomoniasis*. By RAY E. TRUSSELL, M.D., Associate in Hygiene and Preventive Medicine, etc. With an Introduction by E. D. PLASS, M.D., Professor of Obstetrics and Gynecology, State University of Iowa. 277 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$6.00.

# COLLEGE NEWS NOTES

## AMERICAN BOARD OF INTERNAL MEDICINE

### MEMORANDUM TO APPLICANTS FOR ADMISSION TO EXAMINATION

(Revised July 1947)

#### *Organization*

The American Board of Internal Medicine was established in 1936 by joint action of the Section on the Practice of Medicine of the American Medical Association and the Board of Regents of the American College of Physicians. It is a non-profit organization incorporated for the benefit of physicians who, because of their training and experience, desire to be certified formally as specialists in Internal Medicine by a representative group of their colleagues.

The Board consists of twelve members; seven are nominated by the American College of Physicians and five by the Section on Internal Medicine (formerly the Practice of Medicine) of the American Medical Association. Each member of the Board serves for a term of three years but may be nominated and elected for a second term of three years. However, no member may serve for longer than two successive terms. The service is voluntary and members of the Board do not receive compensation beyond the actual expenses incurred at the oral examinations or at special meetings.

#### *Responsibilities of the Board*

The major object of the Board is to pass judgment on the competence of internists who desire certification—not to determine who shall or shall not practice internal medicine as a specialty.

The American Board of Internal Medicine is not concerned with any mechanism which gains special privileges or specific recognition for those physicians who have been certified in internal medicine. It has never been the intent of the Board to define requirements for membership on the staffs of hospitals.

This Board endorses completely the stand of the American Board of Surgery which "specifically disclaims interest in or recognition of differential emoluments that may be based on certification."

#### *Requirements for Admission to Examination and Certification*

Each applicant for certification by this Board must satisfy the qualifications listed below. (I) General Qualifications A, B, C, D. (II) Professional Qualifications A, B, C, D. For exceptions to the requirements C and D under Professional Qualifications, see Page 848, Paragraph G.

##### *I. General Qualifications*

- A. All candidates must be citizens of the United States or Canada.
- B. All candidates must present evidence of satisfactory moral and ethical standing in the medical profession.
- C. All candidates must be active members in good standing in their County and State medical societies in their state of legal residence.

(This ruling shall not apply to commissioned officers of the United States regular Army or Navy while serving outside the territorial limits of the United States.)

D. Canadian citizens applying for admission to examination must be active members of the Canadian Medical Association.

## II. *Professional Qualifications*

A. Graduation from a medical school approved by the Council on Medical Education and Hospitals of the American Medical Association at the date of graduation.

B. Satisfactory completion of an approved internship of not less than twelve months.\*

C. Approved residency or fellowship training in internal medicine according to the following plan (Plan A) or one of the alternate plans described under paragraph D.

*Plan A.* A residency or fellowship in internal medicine for a period of not less than three years in a hospital or other institution approved by the Council on Medical Education and Hospitals of the American Medical Association for residency or fellowship in internal medicine. In addition, two years of practice of clinical internal medicine will be required. The Board will accept the following equivalents as satisfying one year only, of the three years of residency or fellowship to which this paragraph refers.

1. A second year (or a part thereof) of approved internship in a hospital approved for resident training in internal medicine if limited to the medical service (or medical specialties noted under 2) for one year and if recognized as being the equivalent of an assistant residency by the Medical Director of the hospital and the Chief of the Medical Service.

2. One year of approved residency in one of the medical specialties: Allergy, Cardiovascular Disease, Gastro-Enterology, Hematology, Pulmonary Diseases, Neurology, Pediatrics, and Psychiatry.

3. One year of approved residency in Pathology.

4. One year as a graduate student or as an instructor in an approved medical school on a full time basis in Bacteriology, Biochemistry, Pathology, Pharmacology, Physiology, or Internal Medicine.

5. An advanced degree in the fundamental sciences.

*Note:* Graduate training credit for the time involved will be allowed veterans and other candidates who take and satisfactorily complete post-graduate courses in internal medicine or the basic medical sciences provided by accredited medical schools. This ruling shall not apply to courses of less than three months' or more than twelve months' duration. A certificate of creditable performance, based in part, at least, on a formal examination upon completion of the course, will be required.

D. Alternate Training Plans: The Board firmly believes that the plan of intensive training prescribed above offers the best opportunity for a young physician to prepare himself to meet his responsibilities as a specialist in internal medicine. It is recognized, however, that capable individuals may accomplish the same result in a longer period of time during which the training is less intensive. The Board realizes that a number of medical graduates cannot follow the shorter and more desirable plan either because suitable residencies are not available, or in some instances because of personal and economic reasons. Accordingly the Board has modified its previous regulations governing eligibility for admission to examination. In doing so the Board has not modified its standards of examination. It has liberalized its eligibility requirements for admission to examination by accepting half-time formal training, and the practice

\* During the period in which the 9-9-9 program was in effect an approved internship of nine months will satisfy the requirement of twelve months. A residency of nine months is considered as nine months only.

of internal medicine under favorable circumstances as to professional and hospital contacts, in lieu of part of the full-time requirements. It is hoped that by this means exceptional individuals may acquire a knowledge of medicine and experience in its application sufficient to qualify for certification.

The program already described (Plan A), which consists of three years of formal training in an approved residency or its equivalent, following internship, and two additional years in the practice of internal medicine, is recommended by the Board. Variations in this program are now made subject to the following regulations. (See illustrated plans.)

1. In all instances, one year of approved internship and one year of approved residency will be required, except as indicated under Plan "G." The graduate training credit of one year heretofore granted as a result of active duty as a commissioned officer in the Armed Forces during the period beginning December 7, 1941, and ending January 1, 1947 may not be applied in satisfaction of the one year of approved residency referred to in Plans D, E, F, unless the candidate's assignment is considered by the Board to have been equivalent to an approved residency.

2. Following one year of internship and two years of approved residency,\* the remaining requirements may be satisfied by:

(Plan B) That is, by two years of half-time formal training followed by two years of practice limited to internal medicine, or by

(Plan C) That is, by five years of practice limited to internal medicine.

3. Following one year of internship and one year of approved residency, the remaining requirements may be satisfied by:

(Plan D) That is, by four years of half-time formal training followed by two years of practice limited to internal medicine, or by,

(Plan E) That is, by two years of half-time formal training followed by five years of practice limited to internal medicine, or by,

(Plan F) That is, by eight years of practice limited to internal medicine.

4. In every instance at least two years of practice in internal medicine must be included, but in instances in which four years of practice are substituted for one year of residency, only one additional year of practice will be required; when more than eight years of practice are substituted for two years of residency an additional year of practice will not be required.

5. Physicians who have practiced internal medicine for twelve years following an approved internship may qualify for the examinations without further training (Plan G).

Half-time formal training under expanded Plans B, D, and E is defined as follows:

1. Half-time † as an instructor in clinical medicine in a recognized medical school in the United States or Canada.
2. Half-time † in a research fellowship sponsored by a recognized medical school in the United States or Canada.
3. Half-time † as a graduate student in an approved graduate medical school in the United States or Canada.

E. Practice Requirements: A period of not less than two years of practice in the general field of clinical internal medicine or in the more specialized branches of medicine. (See exceptions—Par. 9, Page 846.) This requirement may be satisfied by independent practice or in association with a recognized internist.

\* For the second year of approved residency one of the equivalents described under C may be substituted.

† Certification by the head of department in which the work was done is required.

*Note:* Although in general the Board believes it desirable to complete the three years of formal training before satisfying the requirements of practice a reversal of this order is acceptable.

F. Graduates of Foreign Schools: At the present time neither the Council on Medical Education of the American Medical Association nor any other educational agency in the United States has the machinery to evaluate adequately the quality of foreign medical education. This Board must, therefore, evaluate the fundamental educational credentials and other qualifications of each individual candidate educated abroad who applies for admission to examination. (Requirements for graduates of foreign schools may be obtained on request to the Board—One West Main Street, Madison 3, Wisconsin.)

G. Candidates Graduating Prior to 1937: The requirement of three years of graduate training will not apply to candidates graduating from approved medical schools in the United States and Canada in 1936 or previous thereto, provided such candidates have limited their work to the field of internal medicine for at least two years, and provided each candidate is recognized as an internist by his colleagues in his community.

H. "Preceptor Training": Preceptor type training is not recognized in satisfaction of any part of the three year requirement of formal graduate training.

I. The Board will grant one year of graduate training credit, or one year in satisfaction of the requirements of practice, regardless of assignment, for active duty as a commissioned officer in the United States Army, Navy, or United States Public Health Service for one year or more, beginning on or subsequent to December 7, 1941 and terminating on or before January 1, 1947.

Depending upon the nature of the duty assignments, after January 1, 1947 active duty as a commissioned officer in the United States Army Reserve Corps, United States Naval Reserve Corps, or United States Public Health Service may be applied in satisfaction of one year of the requirements of practice but will not be regarded as satisfying any part of the graduate training requirements, unless the officer is assigned as a resident in Internal Medicine, Neurology, Psychiatry, or Pathology in an Army, Navy or United States Marine Hospital which is approved by the Council on Medical Education and Hospitals of the American Medical Association for resident training in the divisions of medicine referred to.

### *Principles of Training*

The American Board of Internal Medicine is interested in the fact that the candidate has embarked on a career of study voluntarily and has thereby expressed the desire to excel and to participate personally in the world's progress in Medicine.

Preparation must be based on years of continuous thoughtful study. Therefore, in suggesting a program for those who wish advice, the Board hopes to assist the candidates to avoid inferior and superficial programs which may lead to failure and disappointment in later years.

The Board believes that all internists should have a sound fundamental knowledge of Anatomy, Bacteriology, Biochemistry, Pathology, Pharmacology, and Physiology. Such knowledge is essential to the continued progress of any internist. The Board anticipates that adequate training will be obtained in the basic sciences as applied to internal medicine during a formal three year residency program.

The Board wishes to emphasize that time and training are but a means to the end of acquiring a broad knowledge of internal medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to practice internal medicine as a specialty. The responsibility of acquiring the knowledge rests with the candidate. The responsibility of maintaining the standards of knowledge required for certification devolves on the Board.

### *Application*

Candidates for examination must make their application on a prescribed form which may be obtained from the office of the Assistant Secretary-Treasurer.

The application must contain a record of the candidate's premedical and medical training as well as of internships, residencies, graduate study, hospital or dispensary staff appointments, teaching positions, service in the armed forces, membership in medical societies, medical papers published, and the names of three or more well known internists to whom the Board may write for professional and character reference.

The application must be accompanied by one recent, signed photograph of the candidate mounted on the application, and the registration and examination fee of thirty dollars, which fee will cover both the written and oral examinations. An additional fee of ten dollars will be required when the certificate is issued.

### *Method of Examination*

The examinations for certification by the Board comprise two parts: Part I is written; Part II is clinical and is an oral examination. The written examination is held simultaneously in different sections of the United States and Canada on the third Monday of February and October of each year. This examination is divided into a morning and afternoon period for each of which three hours are allowed. The questions asked are framed in such manner as the Board elects; in general, there will be questions designed to test the applicant's knowledge of applied physiology, anatomy, physiological chemistry, pathology, bacteriology, and pharmacology as related to internal medicine, and his basic clinical acumen.

*Candidates must pass the written examination before admission to the oral examination will be authorized.* The oral examination is conducted under the direct supervision of the Board. It is held near the time and place of the annual meetings of the American Medical Association and the American College of Physicians. The examination is conducted at the bedside of the patient. Each candidate is assigned two or more patients and is expected to be sufficiently familiar with whatever problems present themselves to satisfy the Board of his clinical expertness.

### *Reexamination*

Effective January 1, 1946, not more than three written examinations will be authorized. The interval between the first and the second written examinations will be one year. The interval between the second and third written examinations will be not less than two years. A longer period may be required by the Board. A fee of ten dollars is required for each additional written examination.

This ruling does not make it mandatory for a candidate to repeat the examination within one or two years, since each candidate may elect a longer interval.

Not more than three oral examinations are authorized. The interval between the first and second oral examinations will be one year. The interval between the second and third oral examinations will be not less than two years. A longer period may be required by the Board. Candidates may elect a longer interval if desired. A fee of ten dollars is required for each additional oral examination.

### *Certificates*

The certificate issued by the American Board of Internal Medicine shall be in such form as to comply with the articles of incorporation and the bylaws and shall be signed by the officers and members of the Board and shall bear the official seal of the Board.



Certificates of the Board will be issued to candidates who have satisfactorily completed the written and oral examinations and have been found qualified by the Board to practice the specialty of internal medicine. Specialty certification will be designated on the certificate, for those so certified.

### *Advisory Boards*

Allergy, Cardiovascular Disease, Gastroenterology, and Pulmonary Diseases are recognized specialties.

All candidates must pass the written and oral examinations in internal medicine before admission to examination in a specialty of medicine. The specialty examinations are oral only and may be taken the day following the examination in general medicine, or at any other regularly scheduled oral examination.

Applications for consideration in the specialties referred to must be approved by the Advisory Board concerned and confirmed by this Board.

Application forms will be forwarded upon request to the office of the Assistant Secretary-Treasurer, William A. Werrell, M.D., One West Main Street, Madison 3, Wisconsin.

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An orientation course in clinical allergy, to be given by the American Academy of Allergy, under the sponsorship of the University of Michigan Department of Postgraduate Medicine, is a five day course designed to cover the new and pertinent facts of clinical allergy. The faculty will consist of nationally and inter-nationally known men in the field of allergy, and members of the faculty of the University of Michigan Medical School who are qualified to discuss the inter-relationship of allergy to other fields of medicine. Lectures and case demonstrations will be used to illustrate the problems of diagnosis, and modern management of bronchial asthma, seasonal hay fever, allergic rhinitis, atopic eczema, juvenile eczema, migrainous headaches, gastrointestinal allergy, allergic eye disease, contact and occupational dermatitis, allergic blood dyscrasia, and drug allergy. Fee, \$40.00. Registrants: Minimum, 30; maximum, 60. December 8 to 12. Request for further information should be addressed to: Howard H. Cummings, M.D., Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

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A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Tuesday from 7:00 to 9:00 p.m. for twelve weeks, beginning February 7, 1948.

Further information and a copy of the lecture schedule may be obtained upon application to the Office of the Dean, Michael Reese Hospital Postgraduate School, Chicago 16, Illinois.

### ADDITIONAL LIFE MEMBERS

The College takes pleasure in announcing that, on October 11, 1947, the following Fellows became Life Members of the College:

Edgar R. Miller, M.D., F.A.C.P., Wilmington, Del.

Tom B. Throckmorton, M.D., F.A.C.P., Des Moines, Iowa

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The Association of American Physicians will hold its Annual Meeting in Haddon Hall, Atlantic City, N. J., on May 4-5, 1948. The Society for Clinical Investigation will hold its meeting at the same hotel on May 3.

The American College of Radiology will hold its 1948 Annual Meeting on July 20, 1948, at the Sheraton Hotel in Chicago.

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The Colorado State Medical Society will have its 1948 Annual Session September 22-25 at Glenwood Springs, Colorado.

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The Annual Convention of the American Academy of Allergy will take place December 15-17, 1947, at St. Louis, Mo., in the Hotel Jefferson.

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#### U. S. PUBLIC HEALTH SERVICE RESEARCH FELLOWSHIPS

The U. S. Public Health Service will award Research Fellowships for the training and development of medical scientists. A "Pre-doctorate" fellowship is offered with a stipend ranging from \$1200 to \$1600 and tuition a year to holders of the Bachelor's degree who have completed a year or two of their medical course and who desire to devote several years to the study of a basic science before completing their medical studies. A similar fellowship with stipend ranging from \$1600 to \$2000 and tuition is offered for those who have a Master's degree. "Post doctorate" fellowships are available to physicians or holders of the M.D. degree, or Ph.D. degree in a medical science. While tuition costs are not defrayed in these cases, stipends from \$3000 to \$3600, with an increase of \$300 each year, are given. For applicants who meet the requirements for the latter fellowships, and who have special ability or training, there are available "Special research" fellowships. In these cases, the stipend is adjusted to the need. Applications for these fellowships may be secured from the Division of Research Grants and Fellowships of the National Institute of Health, Bethesda 14, Md.

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The State Health Department's Cancer Division of Pennsylvania has allocated \$30,000 to the University of Pennsylvania School of Medicine and Hospital, for the purpose of giving postgraduate courses in the diagnosis and treatment of cancer. The University will give three courses of two weeks each during the 1947-1948 school year on the theory, pathology, diagnosis, and treatment of cancer.

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The Medical Society of Virginia on October 13-15, 1947, at its Annual Meeting at Roanoke, celebrated its 100th Meeting. However, the Society was first organized in the latter part of 1820, and there were some intermissions through the several wars.

Dr. Wyndhand Blanton, F.A.C.P., of Richmond, one of the foremost historians of the Society, gave an address on "1820—The Virginia Doctor and His Times."

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The Twenty-fifth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society was held at Kansas City, October 6-9, inclusive, 1947. Among the guest speakers were the following: Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, "Congenital Hemolytic Jaundice," "Gout," and "Precipitating and Accelerating Factors in Arthritis"; Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill., "Uses and Misuses of the Sex Hormones," "Endocrine Problems in Adolescence," and "The Management of Obesity"; Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio, "Hematemesis and Melena," "The Differential Diagnosis of Jaundice," and "The Diagnosis

of Gastric Cancer"; Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, "How to Prevent Death from Breast Cancer," "Experiences at Bikini," and "Treatment of Deafness in Children by Radium"; Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "Coronary Artery Disease," "Hypertension," and "The Treatment of Congestive Heart Failure"; Dr. Joseph S. D'Antoni, F.A.C.P., New Orleans, La., "Amebiasis," and "The Chronic Diarrheas."

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The Chicago Medical Society has initiated a series of short-term postgraduate medical courses this Autumn by offering a course in cardiovascular diseases, October 2-25, and one in gastro-enterology, October 27 to November 1. The courses were planned by the Society's Committee on Postgraduate Medical Education, of which Dr. Willard O. Thompson, F.A.C.P., is Chairman, and Drs. A. C. Ivy, F.A.C.P., J. Roscoe Miller, F.A.C.P., and John B. Youmans, F.A.C.P., are members. The courses have been organized much along the lines of those pioneered by the College, and the instructional officers include many Fellows of the College from the Chicago area as well as from more distant cities. Designed for specialists and general practitioners alike, the courses were approved for the training of veterans.

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In recognition of the growing importance of alcoholism as a social problem in California, a second Institute on Alcoholic Studies was presented during October at the Los Angeles campus of the University of California. A three-day program, in which social, political, religious, and scientific leaders from California and from the Yale School of Alcohol and Studies participated, covered the following topics: The Problem of Alcoholism in California; Individual and Social Aspects of Alcoholism; Alcoholism as an Individual Problem; Alcoholism as a Public Problem. Among the speakers was Dr. Lawrence Kolb, F.A.C.P., Sacramento, Medical Deputy Director of the Department of Mental Hygiene.

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#### NORTH DAKOTA REGIONAL MEETING

The first Regional Meeting of the American College of Physicians for the State of North Dakota was held at Bismarck, September 13, 1947, under the Governorship of Dr. Robert B. Radl. All but four members from North Dakota were in attendance, and there were a goodly number of guests. An excellent all-day scientific session was held, with an informal reception and dinner in the evening. All present expressed the desire to have the meeting repeated as a yearly occurrence.

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#### IOWA REGIONAL MEETING

\* The first Regional Meeting of the American College of Physicians for the State of Iowa was held at Des Moines on September 27, 1947, under the Governorship of Dr. B. F. Wolverton, F.A.C.P., of Cedar Rapids, and the local Chairmanship of Dr. Maurice J. Rotkow, F.A.C.P., of Des Moines. Thirty-six College members and twelve guests were in attendance. The total College membership of Fellows and Associates for Iowa is fifty-five. Thus two-thirds of the members of the state were in attendance. Dr. Albert M. Snell, F.A.C.P., of the Mayo Clinic at Rochester, Minnesota, was the guest speaker, his subject being "Clinical and Psychological Consideration of Patients with Cirrhosis." At the evening session, Dr. Walter L. Biering, F.A.C.P., of Des Moines, former Regent of the College, spoke on "The American College of Physicians in Retrospect and in Prospect."

## PROGRAMS OF RECENT REGIONAL MEETINGS

The programs of the following recent Regional Meetings of the College are taken, in condensed form, from the printed programs distributed to members of the College in the respective areas. Information concerning registration or special events at these meetings was not available at the time this material went to the press.

*Western New York*

This meeting took place at Syracuse on Tuesday, October 28, under the Governorship of Edward C. Reifenstein, M.D., F.A.C.P. Speakers were drawn from various cities in the newly enlarged Western New York territory. The morning program included papers by the following: Herbert R. Brown, Jr., M.D. (by invitation), Rochester, The Ballistocardiogram and Its Use in Cardiology—Discussion and Motion Pictures; Allan D. Bass, M.D. (Associate), Syracuse, The Use of Mustard Gas in the Treatment of Blood Dyscrasias; Simon Propp, M.D. (by invitation), Albany, Recent Studies of Multiple Myeloma—Results of Treatment with Stilbamidine; George H. Reifenstein, M.D. (Associate), Syracuse, Electrocardiographic Heart Disease; Eugene L. Lozner, M.D. (Associate), Syracuse, The Pathologic Physiology of Hemorrhagic Diathesis; Charles G. Craddock, Jr., M.D. (by invitation), Rochester, Hemophilia—The Report of the Mechanism of the Development and Action of an Anticoagulant in Two Cases; Roger S. Mitchell, Jr., M.D., F.A.C.P., Trudeau, The Value of Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis. The meeting then recessed from the Syracuse University College of Medicine to the Onondaga Golf and Country Club for the remainder of the program. The afternoon session included talks on the following subjects: Pulmonary Ventilation—Its Determination by Four Simple Clinical Methods, by James Monroe, M.D. (Associate), Ray Brook; The Management of Hypertension, Richard H. Lyons, M.D., F.A.C.P., Syracuse; Streptomycin in Pulmonary Tuberculosis—A Preliminary Report, John N. Hayes, M.D., F.A.C.P., Saranac Lake; The Toxic Effect of Streptomycin, Paul Bunn, M.D. (by invitation), Syracuse; Physiological Changes Associated with the Ill Effects of Heat, John H. Talbot, M.D., D.Sc. (by invitation) Buffalo. A clinico-pathological conference was led by J. Howard Ferguson, M.D. (by invitation), Syracuse, with discussion by George M. Mackenzie, M.D., F.A.C.P., Albany, and Ronald L. Hamilton, M.D., F.A.C.P., Binghamton. A reception and cocktails were followed by dinner at the Club. The guest speakers listed were Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., President of the College; Asa L. Lincoln, M.D., F.A.C.P., New York, Governor for Eastern New York; Herman G. Weiskotten, M.D., Dean, College of Medicine, Syracuse University; Albert C. Bickelhaup, D.D.S., Syracuse; and E. R. Loveland, Philadelphia, Executive Secretary of the College.

*New Jersey*

The first New Jersey Regional Meeting of the College was held at the Downtown Club, Newark, on Friday, November 7, under the Governorship of George H. Lathrope, M.D., F.A.C.P. Andrew J. V. Klein, M.D., F.A.C.P., Newark, served as chairman of arrangements. Lewis Barr Flinn, M.D., F.A.C.P., Wilmington, Del., and Asa L. Lincoln, M.D., F.A.C.P., New York, N.Y., College Governors for Delaware and Eastern New York, respectively, presided at the afternoon scientific session. Papers in this program were as follows: Spinal Cord Changes in Pernicious Anemia, with Suggestive Treatment, by Clarence L. Andrews, M.D., F.A.C.P., Atlantic City; Early Detection of Cancer, John E. Leach, M.D., F.A.C.P., Paterson; Probacil Therapy, Walter A. Crist, M.D. (Associate), Camden; Rectosigmoidal Lesions, Johannes F. Pessel, M.D., F.A.C.P., Trenton; Meigs' Syndrome, Abraham E. Jaffin,

M.D., F.A.C.P., Jersey City; Management of the Rheumatic Patient, Jerome G. Kaufman, M.D., F.A.C.P., Newark; Use of Estrogens in Internal Medicine, Elmer L. Sevringhaus, M.D., F.A.C.P., Nutley. Cocktails and a dinner, at which Dr. Lathrope was toastmaster, followed; the guest speaker was George Morris Piersol, M.D., M.A.C.P., Philadelphia, Secretary-General of the College.

### *Kentucky*

The first post-war Kentucky Regional Meeting of the College, under the Governorship of Chauncey W. Dowden, M.D., F.A.C.P., took place at Louisville on Saturday, November 8. General chairman of the meeting was G. W. Pedigo, Jr., M.D., F.A.C.P. In addition to a panel discussion of The Place of Vagotomy in the Treatment of Peptic Ulcer, in which Drs. Samuel A. Overstreet, F.A.C.P., R. Arnold Griswold, F.A.C.S. (by invitation), John D. Trawick, Jr. (Associate), and Hampden C. Lawson (by invitation), participated, the afternoon session at the Louisville General Hospital offered the following papers: Needle Biopsy of the Liver as a Diagnostic Aid in Hepatic Disease, by Herbert M. Clay, M.D. (by invitation); Recent Advances in the Treatment of Blood Dyscrasias and Allied Conditions, Marion F. Beard, M.D., F.A.C.P.; Modern Concepts in the Diagnosis and Treatment of Congenital Heart Disease, Ralph Adams, M.D., F.A.C.S.; all of the foregoing authors from Louisville; Cytological Study of the Sputum in the Diagnosis of Pulmonary Malignancy, Thornton Scott, M.D., F.A.C.P., Lexington. Guest speakers at the banquet at the Pendennis Club were Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., and E. R. Loveland, Philadelphia, Pa., President and Executive Secretary of the College, respectively.

### *Illinois, Indiana, Michigan, Minnesota, and Wisconsin*

The Midwest Regional Meeting of the College occurred on Saturday, November 15, at the Schroeder Hotel, Milwaukee, Wis., with Karver L. Puestow, M.D., F.A.C.P., Governor for that State, as General Chairman, and Francis D. Murphy, M.D., F.A.C.P., as local Chairman of Arrangements. The meeting formed a part of Post-graduate Course No. 8, Internal Medicine, offered under the direction of William S. Middleton, M.D., F.A.C.P., Madison, Wis. The following papers were presented at the first part of the morning session, over which Douglas Donald, M.D., F.A.C.P., Detroit, Governor for Michigan, presided: Liver Biopsy Studies from Peritoneoscopy Specimens, by Merlyn C. F. Lindert, M.D. (Associate), Milwaukee; The Liver in Chronic Ulcerative Colitis, H. Marvin Pollard, M.D., F.A.C.P., Ann Arbor; Cystic Disease of the Liver, George F. O'Brien, M.D., F.A.C.P., Chicago; Results of Lipotropic Therapy in Cirrhosis of the Liver, Frederick Steigmann, M.D., F.A.C.P., Chicago; Recent Studies of Experimental Myocarditis, Franklin A. Kyser, M.D., F.A.C.P., Chicago; End Results in 33 Successfully Treated Cases of Subacute Bacterial Endocarditis with Particular Reference to the Clinical Evidence of Cardiac Efficiency, Walter S. Priest, M.D., F.A.C.P., Chicago; Endocarditis in the Elderly, Eugene F. Traut, M.D., F.A.C.P., Stanley Gumbiner, M.D. (by invitation), Raymond Hench, M.D. (by invitation), and J. Bailey Carter, M.D., F.A.C.P., all of Chicago; The Diagnostic Use of Radioactive Tracers, Kenneth Corrigan, Ph.D. (by invitation), Detroit.

Robert M. Moore, M.D., F.A.C.P., Indianapolis, College Governor for Indiana, presided at the second part of the morning session during which the following offerings were heard: Present Status of Antithyroid Drugs, William H. Beierwaltes, M.D. (by invitation), Ann Arbor; Present Status of Treatment of Toxic Goiter, Willard O. Thompson, M.D., F.A.C.P., Chicago; Gastric Polypi, James B. Carey, M.D., F.A.C.P., Minneapolis; Effect of Enterogastrone on Gastric Secretion in Man, Joseph

B. Kirsner, M.D. (Associate), and Erwin Levin, M.D. (by invitation), Chicago; Prognosis in Recent Myocardial Infarction, Louis N. Katz, M.D., F.A.C.P., Chicago; Enzyme Studies in the Cancer Problem, Van R. Potter, Ph.D. (by invitation), Madison; Studies on the Effect of Estrogens and Androgens on Mammary Cancer, Samuel G. Taylor, III, M.D., F.A.C.P., Danely P. Slaughter, M.D. (by invitation) and Edson Fairbrother Fowler, M.D. (by invitation), Chicago; Follicular Lymphoblastoma, Ovid O. Meyer, M.D., F.A.C.P., Madison.

Presiding officers at the afternoon session were Edgar V. Allen, M.D., F.A.C.P., Rochester, and Cecil M. Jack, M.D., F.A.C.P., Decatur, A.C.P. Governors for Minnesota and Southern Illinois, respectively. The afternoon program consisted of the following presentations: Diagnostic Problems with Fungus Infections of the Lungs, Edwin F. Hirsch, M.D., F.A.C.P.; Treatment of Bronchial Asthma, Leon Unger, M.D., F.A.C.P.; Duration of the Infection Following the Onset of Scarlet Fever, Paul S. Rhoads, M.D., F.A.C.P.; The Value of Vaccination against Epidemic Influenza in the Light of Recent Experience, Clayton Loosli, M.D. (by invitation); Clinical Evaluation of Several Medical Procedures Used in the Treatment of Common Peripheral-vascular Disorders, David I. Abramson, M.D., F.A.C.P.; Some New Theoretical Considerations of Blood Flow, Henry R. Jacobs, M.D., F.A.C.P.; Evaluation of the Present Forms of Treatment of Polycythemia Rubra Vera, Leon O. Jacobson, M.D. (Associate); Protective Action of Penicillin against Bacterial Endotoxins, Walter D. Hawk, M.D. (by invitation), Alden K. Boor, Ph.D. (by invitation), and C. Phillip Miller, M.D., F.A.C.P.; The Development of Bacterial Resistance to Streptomycin, by Dr. Miller; all of the foregoing speakers being from Chicago; Periarthritis Nodosa, Frederick W. Madison, M.D., F.A.C.P., Milwaukee; Classification of Congenital Hypothrombinemia, Armand Quick, M.D. (by invitation), Milwaukee; The Newer Anti-histamine Drugs, Sidney Friedlaender, M.D. (by invitation), Detroit.

The evening program included a reception, and a dinner at which LeRoy H. Sloan, M.D., F.A.C.P., Chicago, Regent of the College, was toastmaster. The list of distinguished guests included Ernest E. Irons, M.D., F.A.C.P., Regent and past President, Chicago; Walter L. Palmer, M.D., F.A.C.P., Chairman of the Board of Governors, Chicago; William S. Middleton, M.D., F.A.C.P., Madison, Regent; and Drs. Robert B. Radl, F.A.C.P., Bismarck, John L. Calene, F.A.C.P., Aberdeen, Joseph D. McCarthy, F.A.C.P., Omaha, Ernest D. Hitchcock, F.A.C.P., Great Falls, Benjamin F. Wolverton, F.A.C.P., Cedar Rapids, and Chauncey W. Dowden, F.A.C.P., A.C.P. Governors for North Dakota, South Dakota, Nebraska, Montana and Wyoming, Iowa, and Kentucky, respectively.

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#### QUESTIONNAIRES RETURNED CONCERNING SAN FRANCISCO ANNUAL SESSION

1361 members of the College have returned the questionnaires distributed in late August asking information about the attendance, program and other items concerning the Annual Session of the College at San Francisco, April 19-23, 1948. The returns indicate that there will be a very representative group from all parts of the United States and Canada in attendance at the meeting. While the majority will travel by railroad, there are some 300 who will go by air, and 200 who will go by automobile. Slightly over 80 per cent of the attendants will be accompanied by their wives or by guest physicians. Fully 600 are interested in a special train or trains which are in the course of arranging by the College. Announcements will follow later. It is now anticipated that a special train will operate from New York City, serving New England, the Middle Atlantic States; another special train from Chicago, accommodating those who will use that gateway; still a third special train is contemplated from the Southeastern, South Central and Midwestern States.

More than 100 are interested in a conducted tour to Hawaii. About three-quarters of this group are interested in making the trip both ways by ship, one-third wish to make the round trip by plane, and the balance are interested in going one way by ship and one way by plane. Arrangements for the Hawaiian trip are in course of preparation and details will be announced later.

A great many valuable suggestions have been received concerning postgraduate courses desired at Los Angeles, San Francisco, Berkeley, Portland, Denver, and other West Coast centers. These suggestions are under consideration by the Committee on Postgraduate Courses.

Many very helpful suggestions were also received concerning the content of the program of clinics, round tables, morning lectures, and general sessions, and those suggestions have been referred to the appropriate committee chairmen.

All members who have thus far not returned the questionnaire are urged to do so, so that adequate arrangements can be made in advance.

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Captain Lloyd R. Newhouser, (MC), USN, F.A.C.P., of the Bureau of Medicine and Surgery, Washington, D. C., has been awarded the Legion of Merit for his distinguished work in developing the Navy's program for obtaining, processing, packaging and distributing plasma and serum albumin during the recent war.

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Colonel Arden Freer, (MC), USA, Ret'd., F.A.C.P., presently an Executive Officer of the Veterans Administration, is a recipient of the Legion of Merit. The award recognizes Dr. Freer's exceptionally meritorious services as Chief of Medical Service and subsequently as Executive Officer, of the Walter Reed General Hospital, and as Director of the Department of Internal Medicine of the Army Medical Center.

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Effective October 1, 1947, Dr. Edward L. Bortz, F.A.C.P., President of the American Medical Association and Governor of the American College of Physicians for Eastern Pennsylvania, became Honorary Consultant to the Medical Department of the United States Navy.

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Dr. Allan Seymour Walker, M.D., F.R.A.C.P., the Official Medical War Historian for Australia, and the first Honorary Secretary of the Royal Australasian College of Physicians, was a visitor to the Headquarters of the American College of Physicians on October 2, 1947.

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The rank of Officer of the French Legion of Honor has been conferred upon C. Charles Burlingame, M.D., F.A.C.P., Hartford, Conn., in recognition of his contributions as Chairman of the American Advisory Board for the American Hospital of Paris, and as an Officer in the Army during the recent war.

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John F. Kenney, M.D., F.A.C.P., Pawtucket, R. I., has been honored by the Memorial Hospital of that city in its adoption of the title "The John F. Kenney Annual Clinic of the Memorial Hospital Internes' Alumni Association." All physicians in Rhode Island, and in nearby cities, were invited to attend the Tenth Annual Clinic on October 29, 1947.

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J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has been honored with an official citation and scroll from the President of Costa Rica, and with the Presidential Medal of Merit (gold and diamond) from the President of Nicaragua.

Roberto F. Escamilla and Richard D. Friedlander, Fellows of the College in San Francisco, have recently been appointed Associate Clinical Professors of Medicine in the University of California Medical School.

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The Joint Committee for the Coördination of Medical Activities, in which the College is represented by Ernest E. Irons, M.D., F.A.C.P. (Chairman) and Walter L. Palmer, M.D., F.A.C.P., met again on August 16, 1947. The discussions at this meeting have been published in full in the Journal of the American Medical Association.

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A fine tribute was paid to a past President of the College on his 78th birthday when, on September 21, 1947, Dr. F. M. Pottenger, Sr., of Monrovia, Calif., received the following statement from the Board of Supervisors of the County of Los Angeles. "It is the feeling of the leaders of the County that the great work you have performed in so sharply reducing the incidence of tuberculosis places the entire community in your debt. A debt that can never be paid except in gratitude and appreciation. We know that tuberculosis is today claiming one-fifth as many lives as it did forty years ago when you began your courageous pioneer efforts in this field. In this sharp reduction your research and your leadership have played a great part."

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The 1947 Assembly of the Interstate Postgraduate Medical Association of North America took place October 14-17 at St. Louis, Mo., under the Presidency of James E. Paullin, M.D., F.A.C.P., Atlanta. The following Fellows of the College were among the speakers at the Assembly: Cyrus C. Sturgis, M.D., Ann Arbor; Elliott P. Joslin, M.D., Boston; Richard B. Capps, M.D., and Leon Unger, M.D., Chicago; John A. Toomey, M.D., Cleveland; Franklin G. Ebaugh, M.D., Denver; Edward L. Bortz, M.D., and John A. Kolmer, M.D., Philadelphia; Walter C. Alvarez, M.D., Rochester, Minn.; Harry L. Alexander, M.D., Goronwy C. Broun, M.D., R. A. Kinsella, M.D., LeRoy Sante, M.D., Daniel L. Sexton, M.D., and August A. Werner, M.D., St. Louis.

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J. Morrison Hutcheson, M.D., F.A.C.P., Richmond, Va., former Vice President of the College, has been awarded the Honorary Degree of L.D. by Hampden-Sydney College.

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Samuel Waldman, M.D. (Associate), Brooklyn, N. Y., has contributed to the College Library of Publications a copy of "Gastroenterology in General Practice," by Louis Pelnor, M.D., with contributions from others, among whom is Dr. Waldman. This book has been published recently by Charles C. Thomas, Springfield, Ill.

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The Medical Society of the State of Pennsylvania offers this year a new departure in refresher courses for general practitioners: a course designed to minimize expense, travel time and interruption of practice. The Society's Committee on Graduate Education, of which Charles W. Smith, M.D., F.A.C.P., Harrisburg, is Chairman, and which includes Robin C. Buerki, M.D., F.A.C.P., Thomas M. Durant, M.D., F.A.C.P., Robert A. Matthews, M.D., F.A.C.P., and Francis C. Wood, M.D., F.A.C.P., all of Philadelphia, has secured a faculty of 150 teachers, largely from medical schools in the state, and outlined a series of ten full-day sessions in each of six cities: Allentown, Harrisburg, Johnstown, Oil City, Wilkes-Barre and Williamsport. These cities, lying across the northern and southern tiers of Pennsylvania were selected also for



their accessibility to physicians remote from the larger medical centers. In each city a day is devoted to each of the following subjects: Neuropsychiatry, Respiratory Diseases and Anesthesiology, Gastro-enterology, Urology, Gynecology and Obstetrics, Cardiovascular Diseases, Skeletal and Muscular Diseases, Skin Diseases and Nutrition, Hematology and Metabolic Disorders, Febrile Diseases and Endocrinology, Modern Therapy. Physiological and pharmacological viewpoints are emphasized. Each course begins in October and ends in May. A topic given in one city on a certain weekday will be repeated in another city on a different weekday, and a registrant may attend the session when and where it is most convenient for him to do so.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to October 15, 1947 inclusive).

Samuel M. Browne, Anderson, S. C. (Col., MC, USA)  
Frederick H. Foucar, New York, N. Y. (Col., MC, USA)  
Gustavus A. Peters, Rochester, Minn. (Major, MC, AUS)

## OBITUARIES

## DR. HORACE WOODWARD CARLE

Horace Woodward Carle, M.D., F.A.C.P., of St. Joseph, Mo., died on April 27, 1947, of pulmonary embolism, chronic heart disease and pneumonia.

Dr. Carle was born at Cincinnati, Ohio, September 22, 1889. He attended school in St. Joseph and was active there in athletics, drama and music. He obtained the degree of Doctor of Medicine in 1914 from the Loyola University School of Medicine and interned at the Kansas City General Hospital. Dr. Carle entered the practice of medicine in St. Joseph in 1915 and shortly thereafter limited his practice to internal medicine. He was a local pioneer in the use of clinical laboratory methods and was recognized as an outstanding leader in his field. Dr. Carle served on the staffs of the Missouri Methodist and St. Joseph's Hospitals, and was a past president of the staff of the former hospital.

A Fellow of the American College of Physicians since 1934, Dr. Carle was also a Fellow of the American Medical Association and a member of the Buchanan County (past president), Missouri State (vice president, 1921), and Southern Medical Societies, American Heart Association and the Kansas City Southwest Clinical Society.

Dr. Carle was a member of the Missouri State Board of Health and Medical Examiners, 1928-32, and president, 1931-32. He served for twelve years on the St. Joseph School Board, and was at one time its president.

## DR. EDWARD L. HANES

Edward L. Hanes, M.D., F.A.C.P., died July 14, 1947, at Altadena, Calif.

Dr. Hanes was born at Chenango Forks, N. Y., in 1871. He graduated from The Albany Medical College in 1899 and served his internship at the New York Lying-in-Hospital. He served on the staff of the Craig Colony for Epileptics, at Sonyea, N. Y., the Hudson River State Hospital, at Poughkeepsie, N. Y., and was a member of the medical staff of the Rochester State Hospital until 1909 when he entered private practice in Rochester. Dr. Hanes was on the consulting staff of the Rochester General Hospital and attending neurologist at St. Mary's Hospital and the Genesee Hospital. During World War I, Dr. Hanes, with rank of major, was in charge of the Neuropsychiatric Division Base Hospital 19, serving overseas. He later served as consultant in neuropsychiatry for the Veterans Administration, and was on the consulting staff of the Rochester State Hospital and of the Craig Colony.

Dr. Hanes was a member and former president of the Rochester Academy of Medicine, and a member of the American Psychiatric Association, Medical Society of the County of Monroe, and the Rochester Pathological Society. Early active in the prevention of mental disease, he was largely responsible for the establishment of the first Mental Hygiene Society in Rochester. He was frequently called upon to testify in important legal trials. Among his publications was a volume, "The Minds and Nerves of Soldiers," in which he reviewed his experiences in World War I.

A founder of the Neuron Club, Dr. Hanes was active in its formative days. A kindly gentleman maintaining the highest ideals of our profession, Dr. Hanes had the respect of all those who knew him.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,  
Governor for Western New York

## DR. FRANCIS EDWARD HARRINGTON

Francis Edward Harrington, M.D., F.A.C.P., died at West Palm Beach, Fla., May 9, 1947. Dr. Harrington was born at Norfolk, Va., June 19, 1879.

A graduate of Gonzaga College, Washington, D. C., Dr. Harrington completed his medical course at the George Washington University School of Medicine in 1904. He then engaged in medical practice and served as part time medical inspector in the Health Department, Washington, D. C., from 1904 to 1910. He was Health Officer of Cumberland, Md., from 1910 to 1914. During the following seven years Dr. Harrington served as Epidemiologist in the U. S. Public Health Service. In 1920 he became Commissioner of Health, Minneapolis, Minn., and in 1921 Director of the Lymanhurst Health Center. Dr. Harrington held appointment in the University of Minnesota Medical School, 1938 to 1945, as Clinical Professor of Preventive Medicine and Public Health, and, from 1945 to 1947, as Clinical Professor Emeritus of that subject.

He had been Vice President of the American Public Health Association and of the American Association of School Physicians, and Secretary of the International Society of Medical Health. He was a member of the Hennepin County Medical and Public Health Associations, the Minnesota State Medical Association, National Tuberculosis Association, Association of Military Surgeons, and a Fellow of the American Medical Association and American College of Physicians.

Dr. Harrington was noted for his kindness in all his relationships with his colleagues and especially for his interest in caring for the welfare of internes and residents in the Minneapolis General Hospital. He was a vigorous fighter for what he thought was right in hospital management and in public health work. One of his major interests was in the detection and prevention of the spread of tuberculosis in the population of Minneapolis. It was for these reasons that he established the Lymanhurst Health Center and fought vigorously for its maintenance and support, often against strong opposition. The recent x-ray survey for tuberculosis in the population of Minneapolis showed a very low incidence of active pulmonary tuberculosis. This excellent result is owing largely to the efforts of Dr. Harrington. As a result of his death his colleagues and friends have lost a fine gentleman and esteemed physician.

EDGAR V. ALLEN, M.D., F.A.C.P.,  
Governor for Minnesota

# ANNALS OF INTERNAL MEDICINE

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## OSTEOPOROSIS \*

By FULLER ALBRIGHT, M.D., *Boston, Massachusetts*

DR. WARING, MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS, AND GUESTS!

OSLER is quoted as saying: "If you know syphilis, you know internal medicine." Time and medicine have marched on. I think if Osler were here today he would agree to amend his statement to read: "If you know the adrenal cortex, you know internal medicine." With this in mind, I first chose, as the subject of this lecture, "Adrenal Cortical Syndromes and Their Diagnoses." But I soon found I did not know the adrenal cortex!

I think I do understand a few things about osteoporosis, which, like everything else, is intimately connected with the adrenal cortex.

### NORMAL INTERNAL DYNAMICS OF THE SKELETON

Before defining osteoporosis, I will give you my working scheme for the normal internal dynamics of the skeleton. I will start by synthesizing a normal middle-aged individual; in so doing I will put in only those structures which concern the present discussion.

First, I will give him an outside skin, and, to add a little realism, four rudimentary appendages (figure 1A); then I will put in a gastrointestinal tract and a kidney with an outlet to the outer world; after that I will fill the body with fluid and set aside one compartment of fluid to represent the blood

\* The John Phillips Memorial Lecture read before the American College of Physicians in Chicago on April 30, 1947. For further studies by the author and his colleagues on the subject of osteoporosis the reader is referred to the following references in the bibliography.<sup>1, 2, 3, 4, 5, 6, 7</sup>

From the Medical Service of the Massachusetts General Hospital and the Department of Medicine of the Harvard Medical School, Boston, Massachusetts.

The expense of these studies was partly defrayed by grants from the Josiah Macy, Jr. Foundation, the Rockefeller Foundation, the National Advisory Cancer Council, Ayerst, McKenna and Harrison, Ltd., and the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council. A bed supported by the Mallinckrodt Chemical Company on the Metabolic Ward was used for part of these studies.

The part of this address which has to do with internal skeletal dynamics and osteoporosis of old age was read at the Ether Centenary at the Massachusetts General Hospital on October 14, 1946.

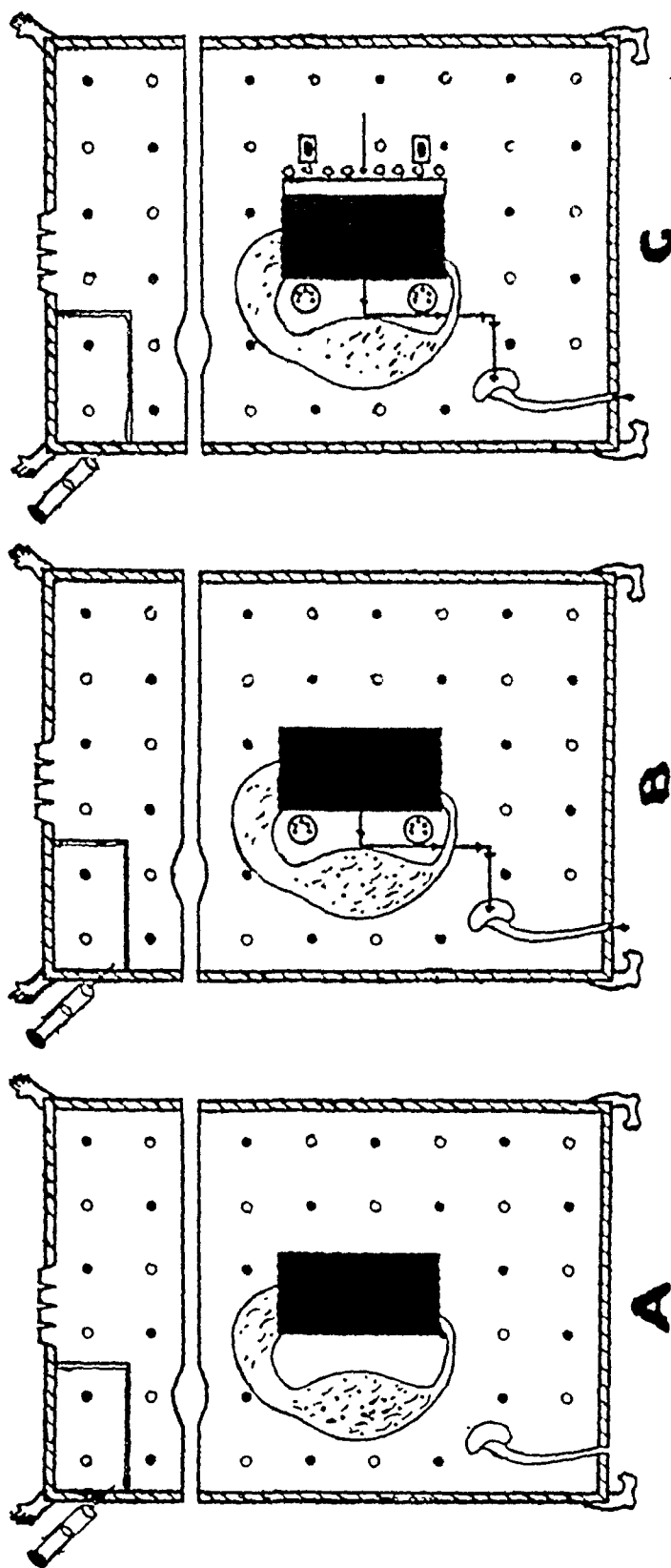


FIG. 1. Diagrammatic synthesis of structures and relationships important for understanding of internal dynamics of skeleton.

(A) Body covering with four rudimentary appendages, four outpocketings to represent teeth, gastrointestinal tract, kidney with outlet to outside, body fluids containing calcium ions (black circles) and phosphate ions (white circles), compartment of body fluids representing serum with a syringe for sampling, a large rectangular black mass representing calcified skeleton, and structure representing muscles attached to skeleton.

(B) Same as (A) plus osteoclasts to represent bone-resorbing surfaces and black arrows to indicate calcium going from bone to kidneys to outside world.

(C) Same as (B) plus osteoblasts on bone-forming surfaces laying down uncalcified matrix, plus localized concentration of phosphate ions on these surfaces and black arrow indicating deposition of calcium therein.

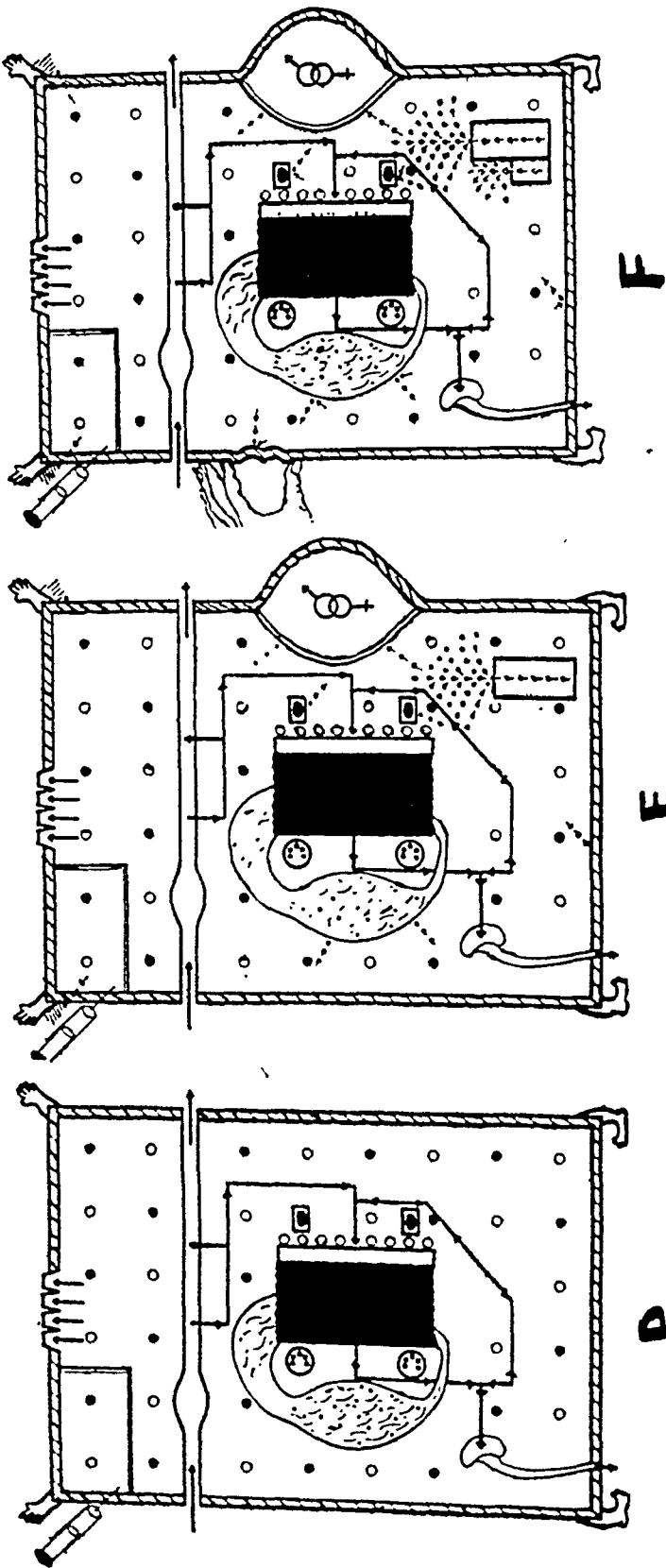


Fig. 1. (D) Same as (C) plus black arrows to indicate movement of calcium in the body.  
 (E) Same as (D) plus steroid-producing organ in right lower quadrant sending out hormones which stimulate axillary hair growth, secondary sex development, osteoblasts, muscle growth, and skin growth.  
 (F) Same as (E) plus special wing of steroid organ producing steroids which inhibit osteoblastic activity, muscle growth, and skin growth (see text).

serum. This component is of importance since it can be sampled with a syringe and thus its chemical constituents can be analyzed. Throughout the body fluids I will put calcium ions represented by black dots and phosphate ions represented by white dots.

I will now introduce into the center of this synthetic man a large black quadrangular area to represent the skeleton (figure 1A). At the two ends of this skeleton I will attach a structure which represents the body musculature. Then, I will introduce outpocketings of the body surface to represent the teeth.

The synthesis now becomes a little bit more complex and, I might add, controversial. The skeleton is composed of an organic matrix into which is deposited a calcium-phosphate-carbonate salt, called dahlite. Much of the skeleton is in the form of a maze of interlacing trabeculae so that the surface area is tremendous. From the point of view of internal skeletal dynamics there are two types of surface—one where bone is being laid down and one where it is being resorbed. Where bone is being resorbed one sees osteoclasts which are large cells with multiple nuclei (figure 1B). It is my belief, not my conviction, that the levels of calcium and phosphate ions in the body fluids are held at such heights by the kidney, in its rôle of regulator of homeostasis, that dahlite is being constantly resorbed at bone-resorbing surfaces. The black arrows (figure 1B) indicate the passage of calcium from bone-resorbing surfaces (indicated by osteoclasts), to body fluids, to kidney, to outside world.

But bone formation and bone resorption occur at one and the same time. Where bone is being laid down one can see osteoblasts laying down uncalcified matrix (i.e. osteoid) and becoming enmeshed as osteocytes in this matrix. Obviously, there must be some local factor which favors the precipitation of the calcium-phosphate-carbonate salt, dahlite, at this point. It is highly probable that there is a localized increase in phosphate ions at bone forming surfaces due to the action of phosphatase or phosphorylase or both in splitting off inorganic phosphate from organic phosphate compounds (figure 1C).

As will be seen below, there are several factors which control the activity of the osteoblasts. However, the most fundamental stimulus is probably "stresses-and-strains" from without upon the skeleton. In this manner the skeleton adds to itself in order to withstand the stresses to which it is put. Furthermore, any surface on which the osteoblasts are building new matrix is insulated by this matrix from body fluids and hence will not be able to act as a bone-resorbing surface.

I will next introduce a series of arrows to indicate the movement of calcium in the body (figure 1D). These arrows speak for themselves. Note that the teeth have only ingoing arrows. One can *acalcify* a tooth but not *decalcify* it.

I will now introduce in the left lower quadrant of my synthetic man a structure to represent the steroid-producing endocrine glands (figure 1E).

These include the male and female gonads and the adrenal cortex. The steroid hormones (see small black arrows) circulate throughout the body and stimulate various structures. Of these, the most spectacular, if not the most vital, are the structures which constitute the secondary sexual characteristics and which give the body many of its contours. It will be noted in figure 1E that they also stimulate muscle growth, skin growth, and bone growth. One almost gets the impression that they stimulate all tissues. However, there is one interesting exception, the hair on top of one's head. This, as shown by Dr. James Hamilton, is inhibited by one of these steroids.

In figure 1F I will introduce a new wing to the structure representing the steroid-producing glands. Here steroid hormones of a different ilk are manufactured. They are represented by arrows with open heads. These steroids have an action opposite to that of the other steroids on certain of the tissues; thus, they inhibit, rather than stimulate, growth of these tissues. Their importance will be brought out later.

This, then, is a normal young man like you and me.

### THE AGING SKELETON

Let us now contrast the bodily structures of our normal young man with those from an elderly individual, say a woman of 60 or a man of 80. The reason for the sex difference will appear shortly.

In examining the elderly individual (figure 2B) one is struck with how many of the changes can be explained on the basis of atrophy. Thus, his skin is thin and when pinched together forms waves with sharp crests as compared with the waves with rounded crests produced when the skin of a normal young man is similarly pinched (figure 2A); the muscle mass and the bone mass are likewise decreased. Moreover, the production of the steroid-producing glands is decreased. The axillary hair is scanty; certain secondary sex characteristics are less prominent than previously; et cetera, et cetera. The teeth are somewhat of an exception. To be sure, many have fallen out because of atrophy of the structure in which they were embedded, or have been pulled out because of decay. The teeth which remain are not atrophied, albeit perchance riddled with caries.

Now let us examine the bone tissue more closely (figure 2B). It will be seen that the decrease in bone mass is due to a decrease in bone formation in the presence of a continued normal degree of bone destruction; in other words, the osteoblasts are not forming new bone matrix as rapidly as in our normal young man (figure 2A). The problem is one of decreased anabolism rather than increased catabolism. It seems probable that this same discrepancy is present in other tissues where we are not so fortunate as to be able to differentiate between decreased formation and increased destruction.

### DEFINITION OF OSTEOPOROSIS

To this form of bone disease where the disturbance is decreased production of osteoid by the osteoblasts is applied the term, "osteoporosis."



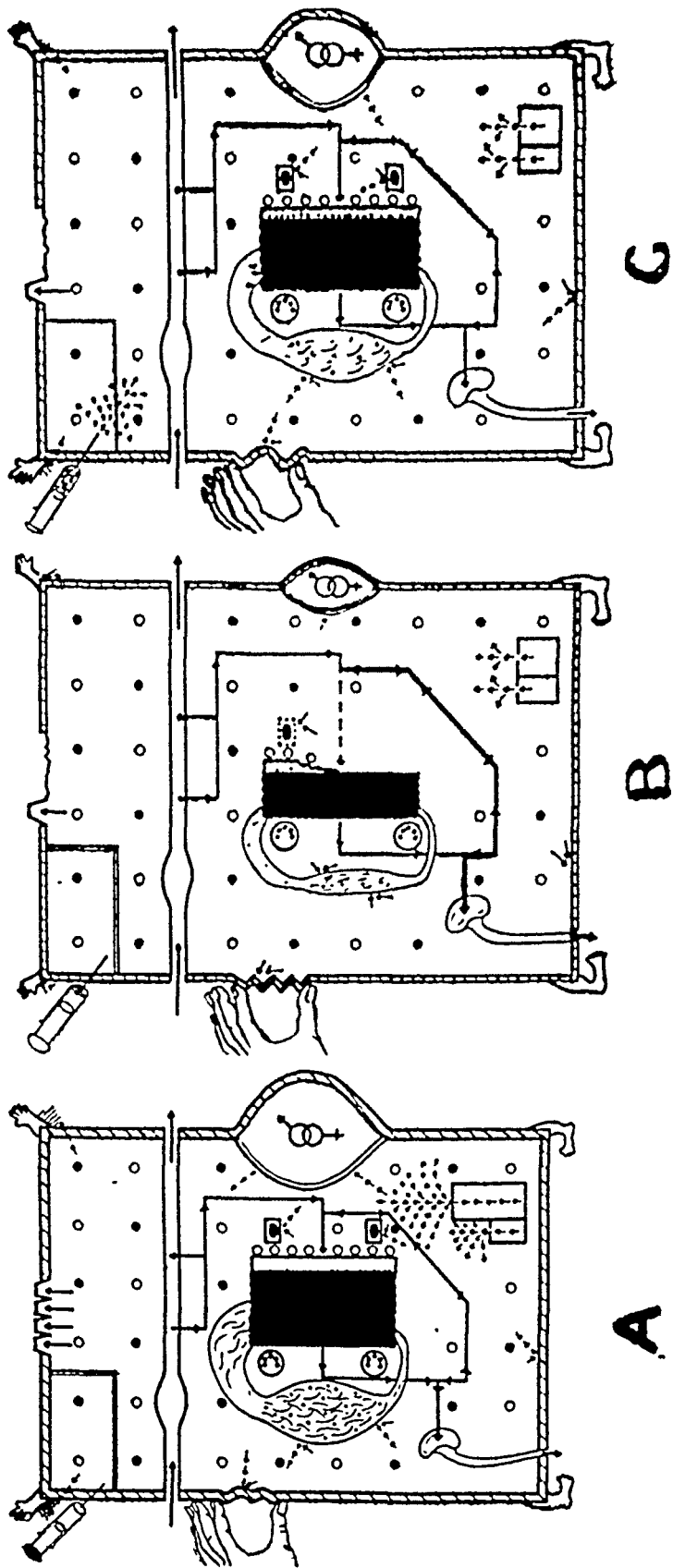


FIG. 2. Diagrams to illustrate senile osteoporosis and effect of steroid therapy. (A) Normal young adult; (B) Senile individual; (C) Senile individual receiving steroid therapy. For further discussion, see text.

The disorder is not primarily one of calcium-phosphorus metabolism but one of tissue metabolism; that bone matrix which is laid down is normally calcified. With continued bone destruction and decreased bone formation, the net result is a loss of calcium from the skeleton and hence an increase in calcium excretion in the urine. Osteoporosis is to be differentiated from two other conditions associated with too little calcified bone mass: osteomalacia, where there is a disturbance of the calcification of the osteoid, and osteitis fibrosa generalisata, where there is increased bone destruction.

### AGES OF ENTRANCES AND EXITS OF CERTAIN STEROIDAL HORMONES

Since the steroids have so important a rôle in the problem at hand, let us examine the production of certain of these in relation to the age of the individual.

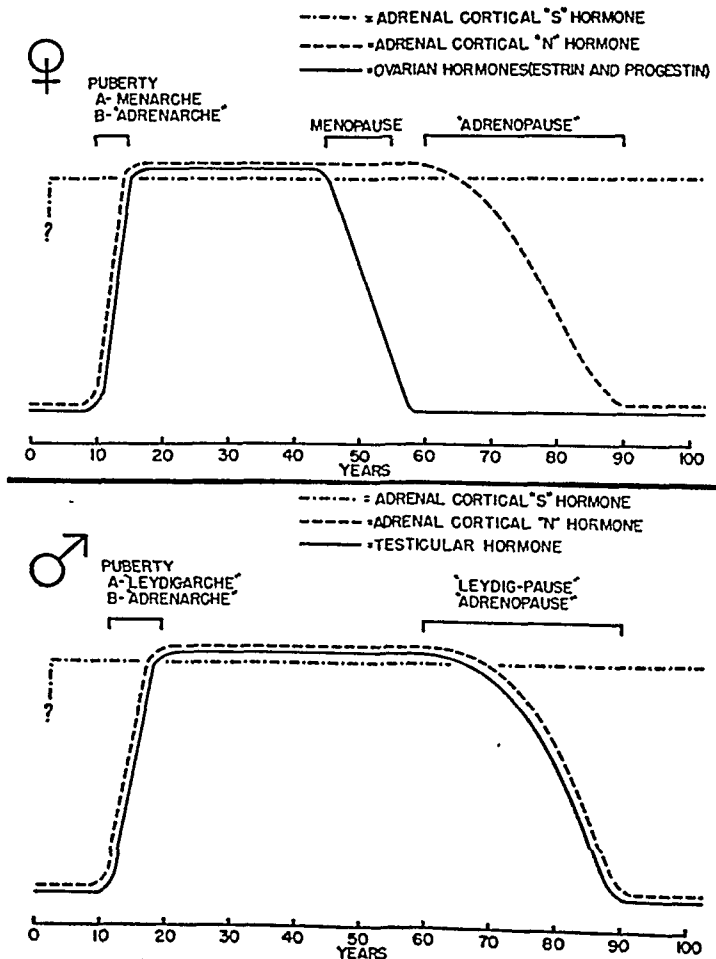


FIG. 3. Schematic diagrams for the female and the male to show their approximate ages at the times of entrance and exit of certain steroids on and off the scene.

In the female (figure 3) the ovarian hormones, estrin and progesterin, are first produced in any quantity at the menarche. Their production falls rather precipitously at the menopause. Our knowledge concerning these

two hormones is facilitated by the fact that their presence is indicated by the menstrual cycle.

There is another key steroid hormone about which our knowledge also is quite clear. I speak of the adrenal cortical steroid hormone which has a somatotrophic action somewhat similar to the male gonadal hormone, testosterone, and the production of which in the female governs the growth of axillary and pubic hair and the excretion of 17-ketosteroids in the urine. I will call this hormone the adrenal cortical "nitrogen" or "N" hormone. The onset of its production is usually fairly synchronous with those of estrin and progesterin and the manifestations produced by all three are usually attributed to one factor, namely, puberty. But in certain instances the onset of production of the "N" hormone is dissociated from the others. A patient with Addison's disease can have a normal menarche with regular periods, normal breast development, etc., but grow no axillary or pubic hair. Dr. Lawson Wilkins of Baltimore has told the speaker that he has seen a group of seven children in which the axillary and pubic hair production started very precociously whereas the menarche came at the usual time. Then, in the condition, ovarian agenesis, where the ovarian tissue is congenitally lacking, the production of axillary and pubic hair and of 17-ketosteroid precursors, in many instances, appears at the normal time for the menarche, albeit in reduced amounts for reasons which need not be discussed now.<sup>6</sup> In short, there is an "adrenarche"-with-respect-to-the-"N"-hormone without a menarche. The production of axillary and pubic hair and of 17-ketosteroid precursors continues after the menopause, from which I infer that the "adrenopause"-with-respect-to-the-"N"-hormone and the menopause are not simultaneous. None the less, there is an "adrenopause," as very elderly women have very scanty axillary and pubic hair and very low 17-ketosteroid excretions in the urine.

Now let us turn to the male. Since the androgens made by the interstitial cells of Leydig of the male gonads have an action similar in certain respects to that of the adrenal cortical "N" hormone, it is impossible as yet to draw a time-curve differentiating the two hormones. In other words, one cannot differentiate the "Leydigarche" from the "adrenarche." In all probability the gonadal hormones and the adrenal cortical "N" hormone start at the same time at puberty. They cease, not at the time of the female menopause, but probably at the time of the female "adrenopause" (figure 3).

In figure 1F it was pointed out that our normal young man possesses two types of steroids: one which stimulates anabolism and one which inhibits anabolism. The best and perhaps the only example of the latter type of steroid is the adrenal cortical "sugar" or "S" hormone. This is the hormone that promotes the breakdown of lymphoid tissue and thereby the release of immune globulin, that interferes with the burning of sugar by inhibiting the action of hexokinase, that facilitates deposition of glycogen in the liver; this is the hormone that in excess produces Cushing's syndrome, the hormone

that is most responsible for the manifestations of the adaptation syndrome of Selye,<sup>9,2</sup> the hormone, the production of which by the adrenal cortex is under the control of the adrenocorticotrophic hormone (A.C.T.H.) of the pituitary; this is the steroidal hormone that has an oxygen on the 11th carbon atom and for which the "11-oxycorticosteroid" (11-OCS) determination of Talbot, Saltzman, Wixom, and Wolfe<sup>10</sup> is a quantitative expression. I do not know about infancy, but otherwise the production of "S" hormone is present throughout life (figure 3). Its property of antianabolism may be due to some disturbance in building amino acids into protoplasm or to a shortage of amino acids because of their increased conversion into glycogen in the liver, or to any one of a dozen other possibilities.

#### STEROIDAL INBALANCES AS CAUSES OF OSTEOPOROSIS

1. Old Age. In looking for the cause of the atrophy of multiple tissues in our elderly individual (vide supra) the question arises whether atrophy of those glands producing anabolic steroids occurs first, and leads secondarily to atrophy of other organs, or whether old age per se causes atrophy of all tissues. This question can be put to the test. If the atrophy is secondary to decrease in steroid production, it should respond to steroid therapy (figure 2C). It does, at least to a certain degree. We have shown that testosterone propionate stimulates protoplasmic anabolism with retentions of nitrogen, phosphorus, potassium, and sulfur in the proportions in which they are found in protoplasm (figure 4); but, what is more pertinent to the present discussion, the atrophy of bone which occurs in old age is offset by the administration of estrogens and/or androgens (figure 5).

*The first cause of osteoporosis on a steroidal basis, therefore, is old age with its atrophy of bone as one of multiple tissues; this atrophy is at least partly attributable to decreased production of anabolic steroids in the presence of continued production of anti-anabolic steroids.*

2. The Post-Menopausal State. From the discussion above it is seen that senility is ushered in by a puberty in reverse. It is further seen that there are at least two steps in the turning-off of steroid production in the female, the menopause and the "adrenopause." Since estrin has a marked effect in stimulating osteoblasts (figure 6), the first of these steps is followed by osteoporosis. The relatively early onset of the menopause accounts for the fact that osteoporosis is so much more common in females.

*A second etiology for osteoporosis on a steroidal basis, therefore, is the post-menopausal state where the cause is a lack of estrin production.*

3. Cushing's Syndrome; Adaptation Syndrome of Selye; Administration of Adrenocorticotrophic Hormone (A.C.T.H.). I have mentioned two conditions where osteoporosis is due to lack of anabolic steroids; essentially the same situation can be brought about by an excess of the anti-anabolic-adrenal-cortical "S" steroid such as one meets in Cushing's syndrome and during the stage of resistance of the adaptation syndrome of Selye or after the administration of A.C.T.H.

In figure 7B the speaker's interpretation of the pathological physiology of certain aspects of the adaptation syndrome and of Cushing's syndrome is shown diagrammatically. Until recently I have felt that the *modus operandi* of testosterone in offsetting this disordered physiology was by virtue of

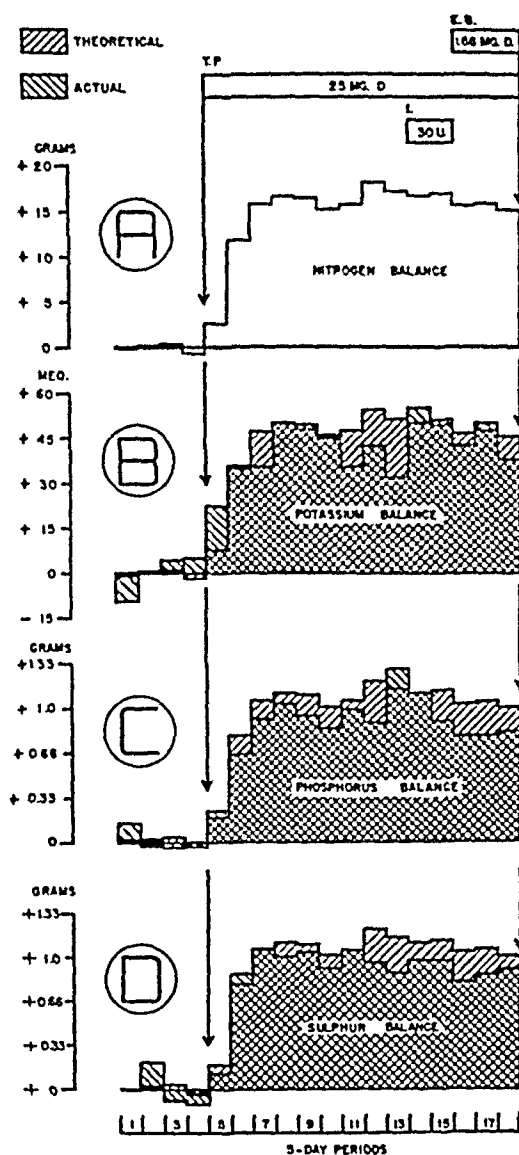


FIG. 4. A comparison of deviations in the nitrogen balance with those of the potassium, phosphorus, and sulfur balances as a result of testosterone propionate therapy in a patient with Cushing's syndrome (B.V., No. 74372).

The balances are charted as deviations from the averages of the four control periods. T.P. = testosterone propionate; L = insulin; E.B. = estradiol benzoate; D. = dosage per day; U. = units per day. The data for potassium are based on analyses of urinary excretion alone.

The chart has four divisions: A = the measured nitrogen balance; B = the measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the potassium balance; C = measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the phosphorus balance (after the phosphorus theoretically retained with calcium had been subtracted); D = measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the measured sulfur balance. This study has been published elsewhere in more detail.<sup>4,6</sup>

overcoming an anti-anabolic effect by the introduction of an anabolic effect. A second possibility will be discussed below.

In figure 8 the effect of testosterone propionate therapy in reducing the calcium excretion in a female patient with Cushing's syndrome is illustrated.

It is probably premature to discuss the action of A.C.T.H. since this substance has been available a short time only and the observations require checking. Since A.C.T.H. presumably releases "S" hormone from the

M.H. MALE 278511  
SENILE OSTEOPOROSIS  
1/1/41

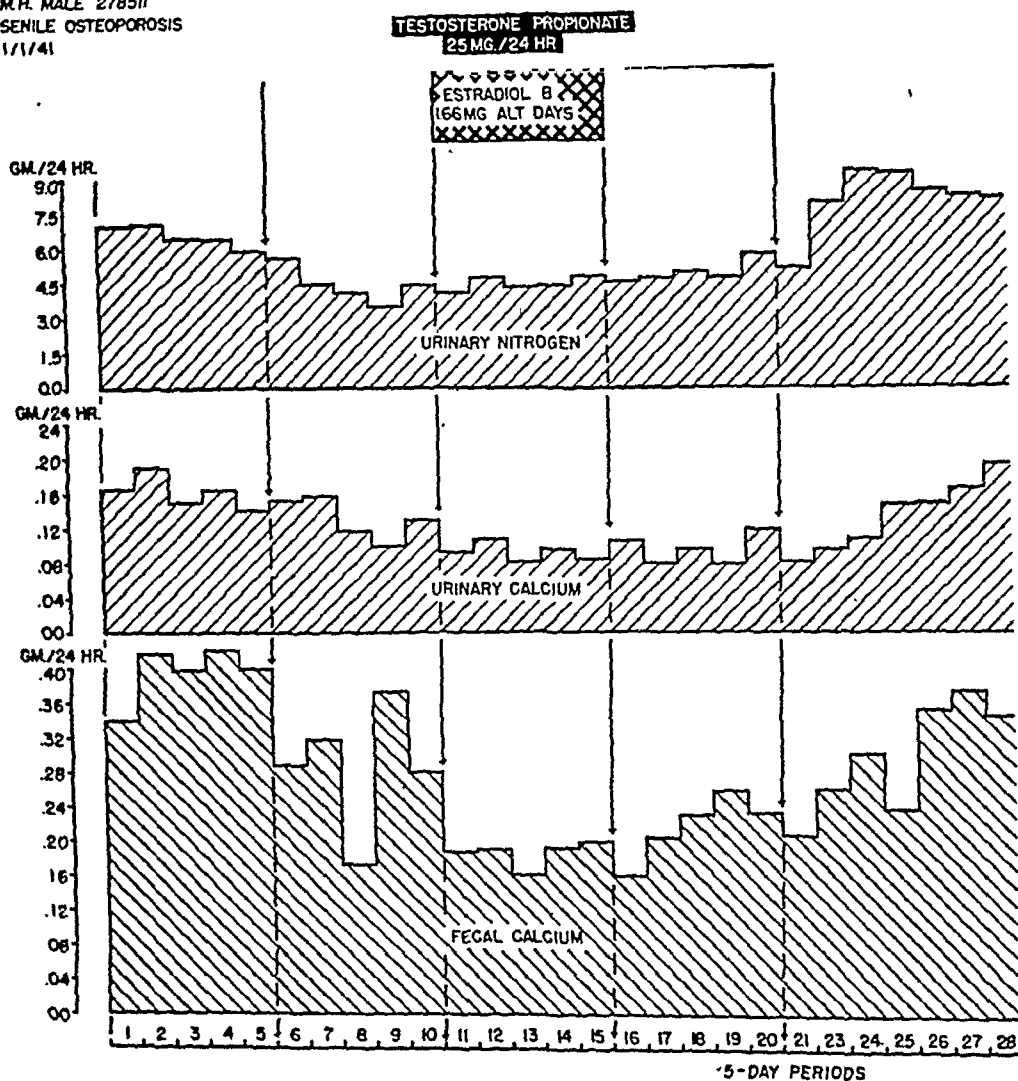


FIG. 5. Effect of testosterone propionate alone and in combination with estradiol benzoate on urinary nitrogen excretions and on urinary and fecal calcium excretions of a patient with senile osteoporosis.

The patient (M.H., No. 278511) was on a constant intake throughout the 28 five-day periods. Note the marked reduction in nitrogen excretion on the administration of testosterone propionate and the rebound when testosterone propionate was omitted; and that estradiol benzoate had no effect on the nitrogen excretion. Note that testosterone propionate reduced both the fecal and urinary calcium excretions and that estradiol benzoate further reduced both of the excretions. A more complete discussion of this study will be found elsewhere.<sup>5</sup>

S.B. 430664 FEMALE AGE 60  
OSTEOPOROSIS  
10/27/45

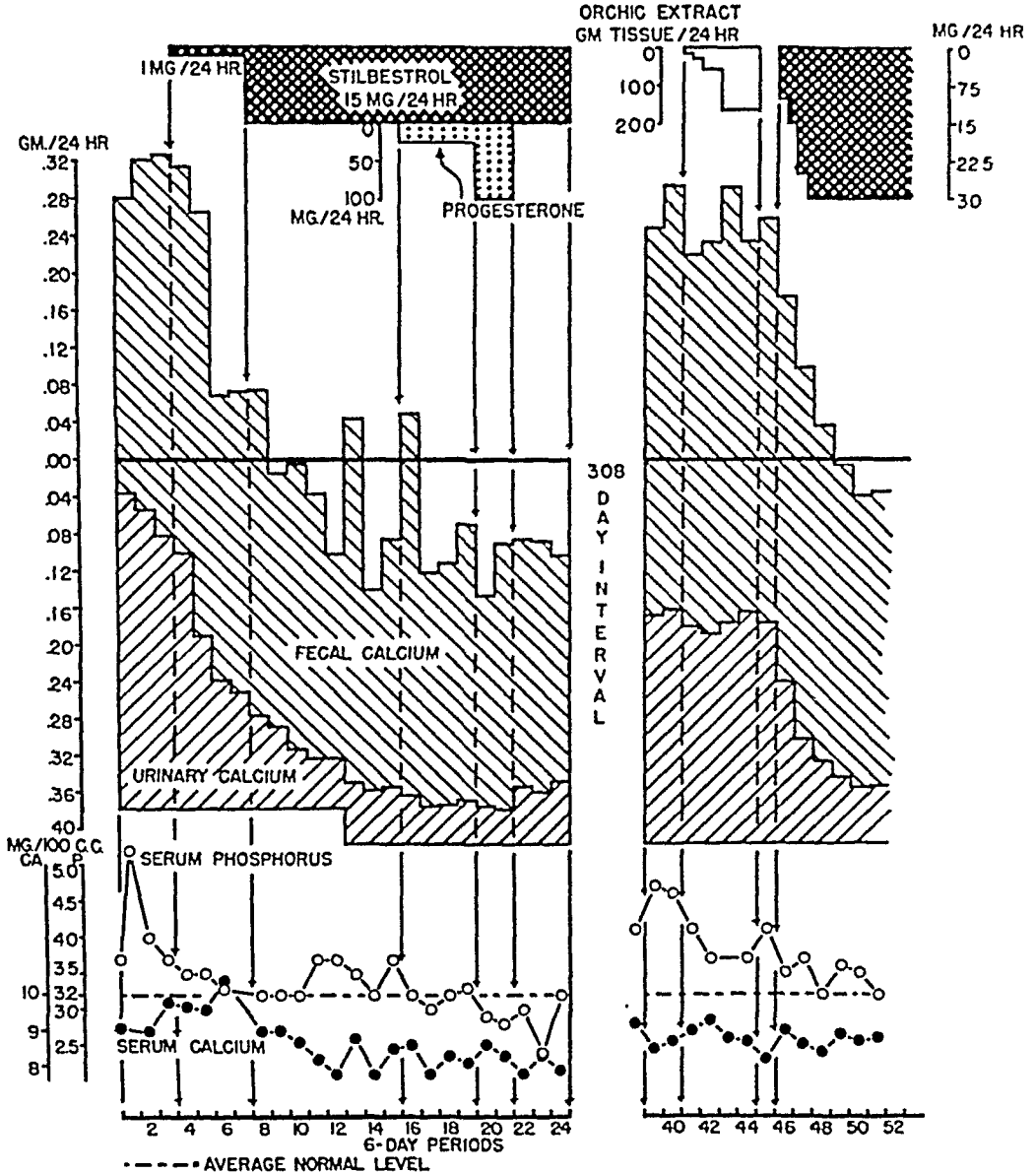


FIG. 6. Effect of diethylstilbestrol at various dose levels on calcium metabolism of a patient with post-menopausal osteoporosis complicated by Paget's disease.

Metabolic data in this figure are arranged according to the following scheme. There is a horizontal base line; intake is charted on a reverse scale downward from this base line; urinary and fecal excretions are measured from the intake line upward toward the base line; thus, a positive balance is indicated by a clear area below the base line; a negative balance by a hatched area above the base line.

Note marked fall in urinary calcium excretion with diethylstilbestrol; note, furthermore, that 30 milligrams daily is not much more effective than one milligram daily (compare metabolic periods 4 through 7 with periods 46 through 49). Note that serum phosphorus level tends to fall on therapy; that the addition of progesterone to the diethylstilbestrol medication (periods 16 through 21) had no marked effect. The "orchi extract" given in periods 41 through 44 was apparently without effect and need not be discussed further here. For more detailed discussion of the first 24 six-day metabolic periods see a previous publication.<sup>5</sup>

adrenal cortex, with a potent preparation of A.C.T.H. one is in position to study the initial effect of "S" hormone. By the time one sees a patient with Cushing's syndrome secondary changes have set in and one cannot tell which is the cart and which is the horse. The quantity of "S" hormone, itself, available is too small to allow decent metabolic studies on human beings.

In figure 9 the effect of A.C.T.H. on a male patient, 41 years of age, suffering from mild panhypopituitarism (chromophobe pituitary adenoma) is shown.\* It will be noted that with A.C.T.H. administration there was a marked but poorly sustained rise in nitrogen, phosphorus, and potassium

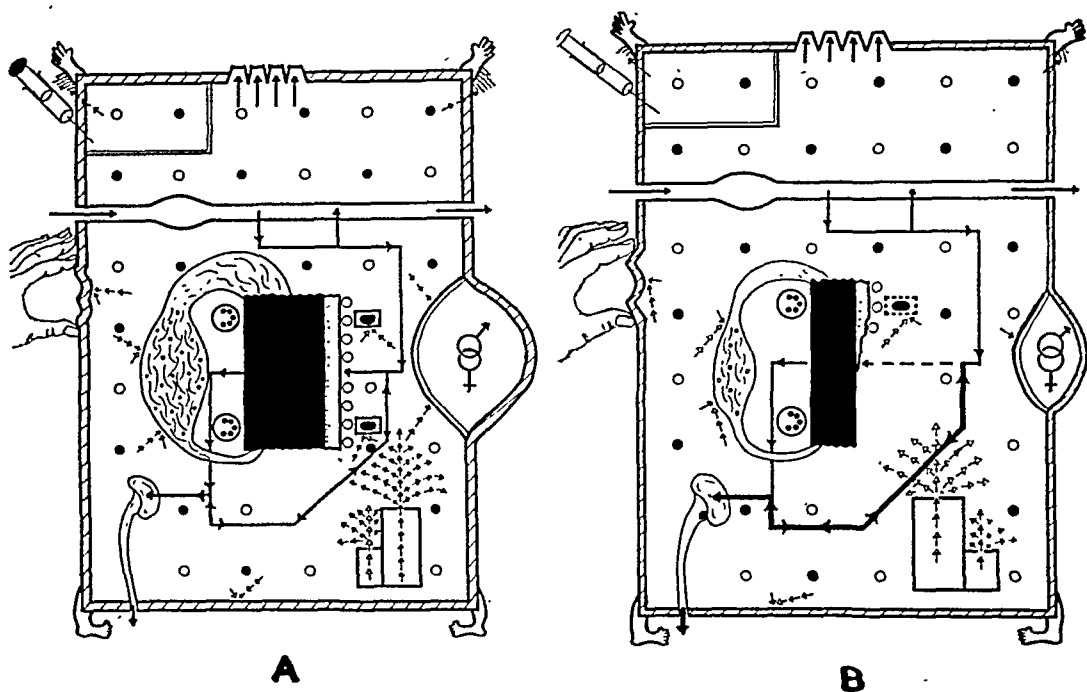


FIG. 7. Schematic diagram to compare pathological physiology of Cushing's syndrome and adaptation syndrome of Selye (B) with the normal (A).

The decrease in the production of anabolic steroids depicted in this figure is more compatible with the adaptation syndrome than with Cushing's syndrome; both syndromes have in common the over-production of the anti-anabolic steroid.

excretions. The same was true of the 11-oxysteroid and 17-ketosteroid excretions which are not charted. Directly concerned with the present discussion, however, is the striking rise in the urinary calcium excretion which was better sustained than that of the other substances measured. Moreover, during the second course of A.C.T.H. administration (period 10), when there was no rise in nitrogen excretion, there was a definite increase in calcium excretion.

*A third cause for osteoporosis on a steroidal basis, therefore, is the group of conditions—Cushing's syndrome, adaptation syndrome of Selye, and the*

\*The A.C.T.H. for this experiment was supplied by Dr. John Môte of the Armour Company. These studies were carried out in conjunction with Dr. Frederic Bartter and Dr. Anne P. Forbes.



*patient receiving A.C.T.H.: in the triad the one common denominator is an over-production of adrenal-cortical "S" hormone.*

From the above discussion it is seen that there are three steroidal hormones stimulating the osteoblasts (adrenal cortical "N" hormone, estrogen, and testosterone) and one steroidal hormone inhibiting the osteoblasts (adrenal cortical "S" hormone). In the normal female and normal male these hormones are in balance (figure 10); in the post-menopausal state, old

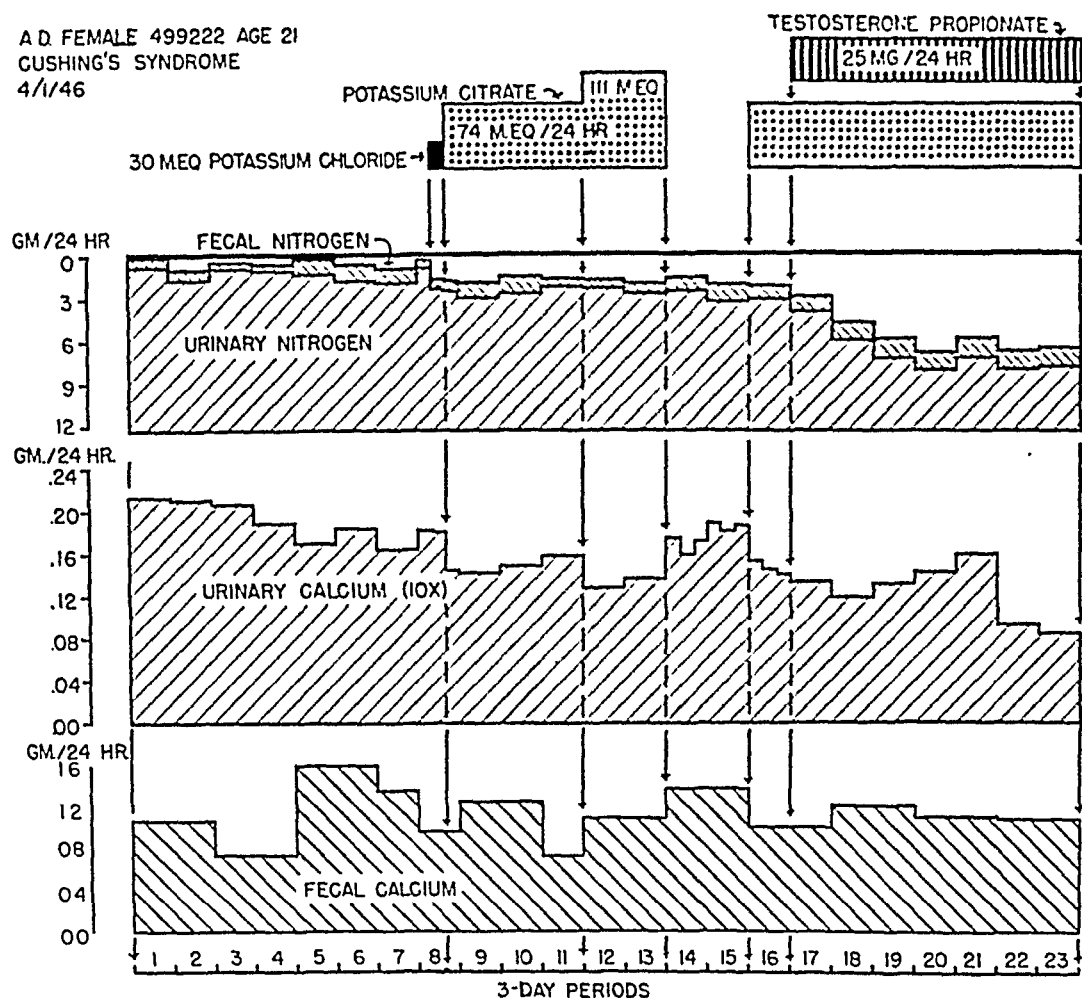


FIG. 8. Metabolic study to show effect of testosterone propionate in decreasing calcium excretion in a patient with Cushing's syndrome.

The study entailed 23 three-day periods on a constant intake. Selected for this figure are the nitrogen metabolic data and the urinary and fecal calcium excretions. The nitrogen metabolic data are charted according to the scheme outlined in the legend to figure 6. Note the marked fall in the urinary nitrogen and calcium excretions during testosterone propionate therapy (periods 17 through 23). Attention might be called—although no further comments on it will be made—to the definite decrease in the urinary calcium excretion and the suggestive decrease in the urinary nitrogen excretion with an increase in potassium intake.

This study was carried out on patient A.D., No. 499222, aged 21, with classical Cushing's syndrome resulting from adrenal cortical hyperplasia as shown by operation (see also figure 11); the data have not yet been published; they were collected in conjunction with Dr. Edward C. Reifenstein, Jr., Dr. Frederic C. Bartter, and Dr. Anne P. Forbes, and it is anticipated that the complete study will be published later in conjunction with these colleagues.

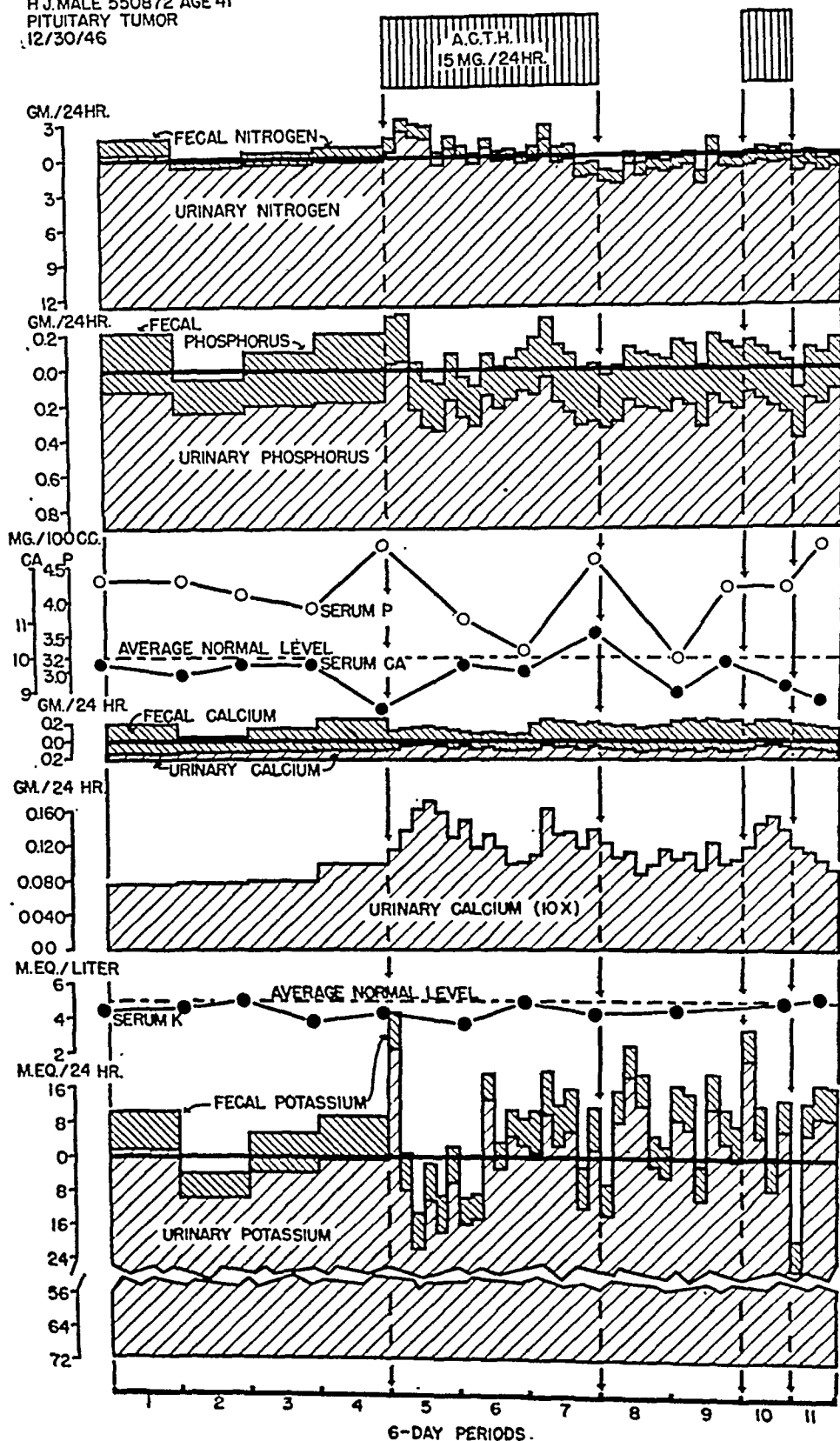


FIG. 9. Metabolic study showing effect of A.C.T.H. on a patient with panhypopituitarism secondary to a chromophobe adenoma.

Charted are the nitrogen, phosphorus, calcium, and potassium metabolisms; the serum phosphorus, calcium, and potassium levels; and a magnified version of the urinary calcium excretion by itself. For further discussion, see text. It is anticipated that the complete study will be published in the near future.

age in either sex, and Cushing's syndrome these hormones are out of balance (figure 10) and osteoporosis results; in panhypopituitarism the hormones are all markedly reduced but the balance is maintained so osteoporosis does not result (figure 10).

*Mode of Action of Testosterone Propionate in Causing Protoplasmic Anabolism.* There is abundant evidence that the administration of testosterone propionate promotes tissue anabolism. It has been assumed that this is a direct stimulating action on anabolic processes. Thus, testosterone promotes growth in the combs of capons when administered topically. There may, however, be another mechanism. It has been shown in Dr. Edward Dempsey's laboratory that the administration of testosterone propionate to rats leads to decreased steroids in their cortices.\* Venning and Browne<sup>12</sup> found a fall in the adrenal cortical "S" hormone excretion (biological assay)

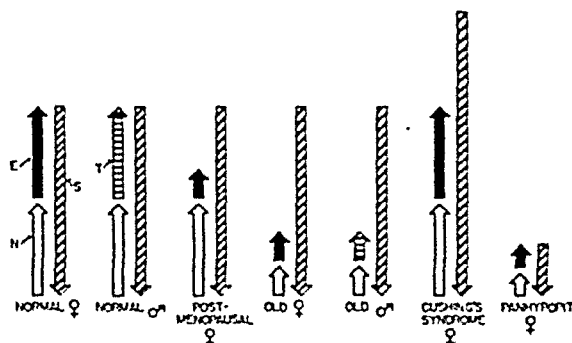


FIG. 10. Schematic diagram to show effect of certain steroidal hormones on osteoblastic activity.

E. = estrogen; N. = adrenal cortical "N" hormone; S. = adrenal cortical "S" hormone; T. = testosterone. An arrow pointing upward represents a stimulating effect; an arrow pointing downward represents an inhibiting effect. For further discussion, see text.

following the administration of testosterone propionate. Talbot, Albright, Saltzman, Zygmuntowicz and Wixom<sup>13</sup> have reported a fall in 11-OCS excretion following administration of testosterone propionate.

In figure 11 are shown on a female patient of 21 with Cushing's syndrome the effect on the 11-OCS and 17-KS excretions of a high-protein diet, added potassium citrate, testosterone propionate, and two adrenal explorations. Pertinent to the present discussion are the following observations on this patient: (1) the marked fall in 11-OCS excretion under administration of testosterone propionate (see days 86 through 107), (2) the failure of the 11-OCS excretion to rise following the first operation when the patient had been receiving testosterone, and, (3) the rise in 11-OCS excretion after the second operation when the patient had not been receiving testosterone.† Dr. Edward Dempsey reported that both adrenal cortical biopsies showed

\*The steroids are studied for three properties: (1) birefringence, (2) reaction to Schiff's stain, and (3) reaction to Sudan stain.

†A rise in 11-OCS excretion following trauma and hence following an operation is the expected finding; the rise is increased in patients with Cushing's syndrome.

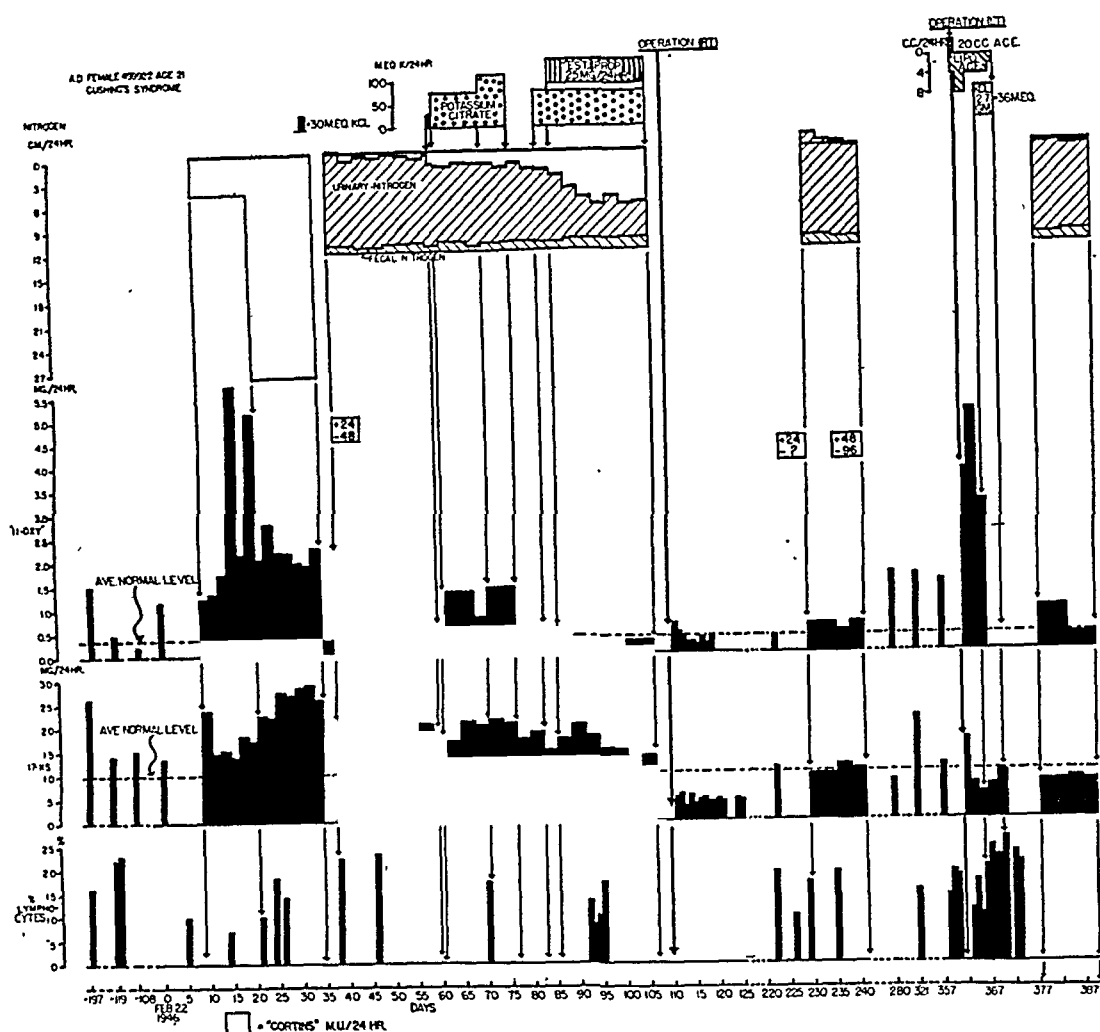


FIG. 11. Study on a patient with Cushing's syndrome to show effect of various procedures, notably administration of testosterone propionate, on the 11-oxycorticosteroid and 17-ketosteroid excretions and the percentage of lymphocytes in the blood smear.

The figure includes the nitrogen intake by itself from day 8 to day 35, the total nitrogen metabolism (urine, feces, and intake) from day 37 to day 107, from day 228 to day 240, and from day 377 to day 389. Data presented in figure 8 are derived from the same study and represented days 37 to 107.

Of special concern to the present discussion are the 11-oxycorticosteroid excretions. Note that, in spite of wide fluctuations, they tend to be high throughout, that they fall to the normal range with testosterone therapy, that there is virtually no rise following the first adrenal exploration (day 110), but that there is a marked rise following the second operation (day 361); note in this connection that the patient was receiving testosterone propionate up to the first operation, but not before the second operation. For further discussion of 11-oxycorticosteroid excretions in this case, see text.

There are also included in the figure the results of three assays of 11-oxycorticosteroids by the biological method. All three values are high, the normal individual being positive for three and negative for 24 mouse units per day.

The 17-ketosteroid excretion and the percentage of lymphocytes in the smear do not particularly concern the present discussion. It should be pointed out, however, that, with the administration of testosterone propionate, the 17-ketosteroid excretion does not rise; this indicates that its endogenous production in the adrenal cortex is decreased sufficiently to offset the increase from the exogenous source.

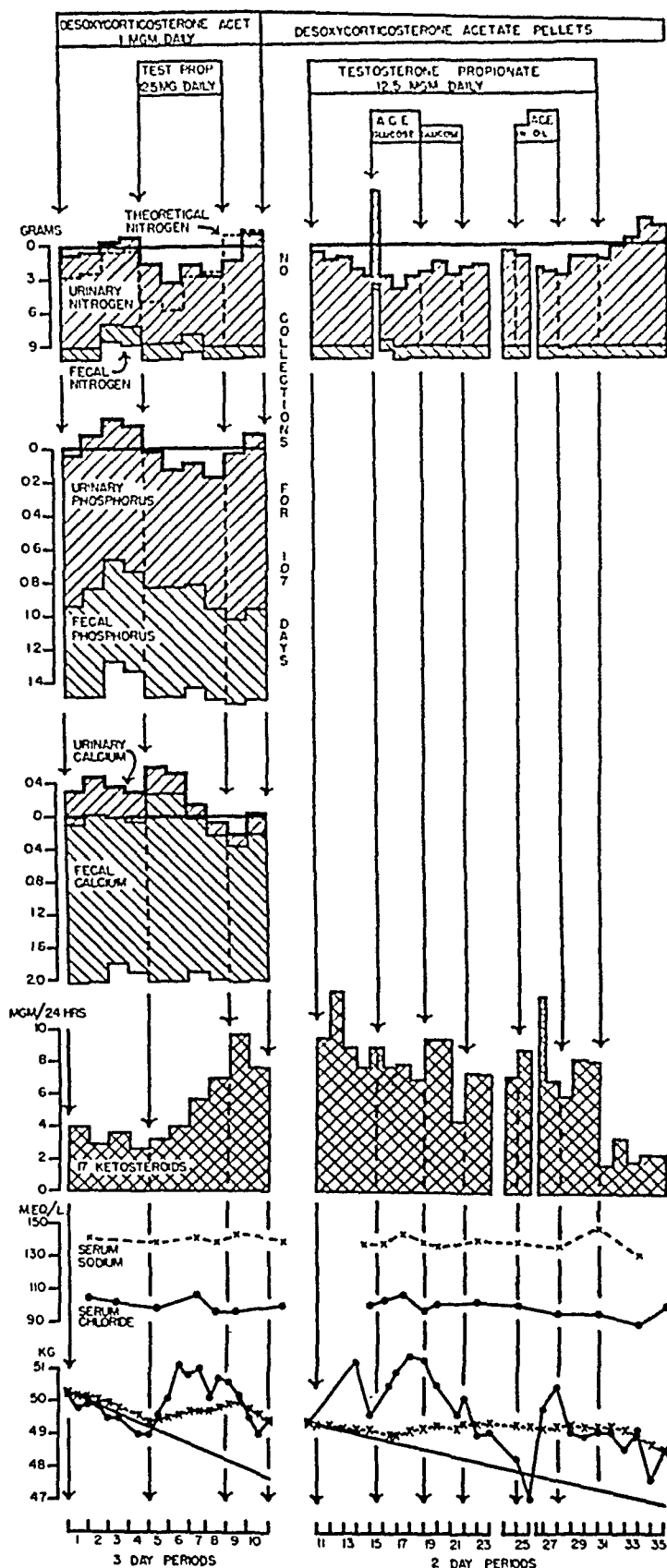


FIG. 12. Metabolic study on patient with Addison's disease to show that testosterone propionate can exert its somatotropic action in the absence of the adrenal cortex.

The study is divided into two parts with an interval of 107 days. The first part consists of 10 three-day metabolic periods, the second of 25 two-day metabolic periods. During the first part of the study the patient received desoxycorticosterone acetate, one milligram daily intramuscularly; before the second part of the study she had been implanted with desoxycorticosterone acetate pellets. The nitrogen, phosphorus, and calcium metabolic data are arranged according to the scheme used in figure 6. A.C.E. = adrenal cortical extract.

Note the decrease in nitrogen (both parts of the experiment), phosphorus, and calcium excretions on the administration of testosterone propionate and the rebound in the excretions when this substance was omitted. The unexpectedly high 17-ketosteroid excretion (circa three milligrams per day) for a female patient with Addison's disease is to be explained by an interfering, non-specific ketone. This value was wiped out when the extract was put through Girard's reagent. The weight curves at the bottom of the figure do not concern the present discussion. The curve connecting black circles represents the actual weight. The curve connecting "X's" represents the "theoretical-weight-based-on-nitrogen."<sup>6</sup>

The data shown in this figure pertain to patient S.G., No. 385496, and were collected in conjunction with Dr. Edward C. Reifstein, Jr., Dr. Laurence Kinsell, and Dr. Anne P. Forbes.

hyperplasia but that the first biopsy showed the zona fasciculata devoid of the cortical steroids, whereas the second biopsy showed this tissue filled with steroids. It would appear that testosterone therapy depleted the cortices of steroids, thus lowering the 11-OCS excretion and making impossible a post-operative release of said hormone. To be sure, the patient received Upjohn's lipo-adreno-cortical extract following the second operation, but it is very unlikely that this could account for the high value of 11-OCS excretion at that time (figure 11).

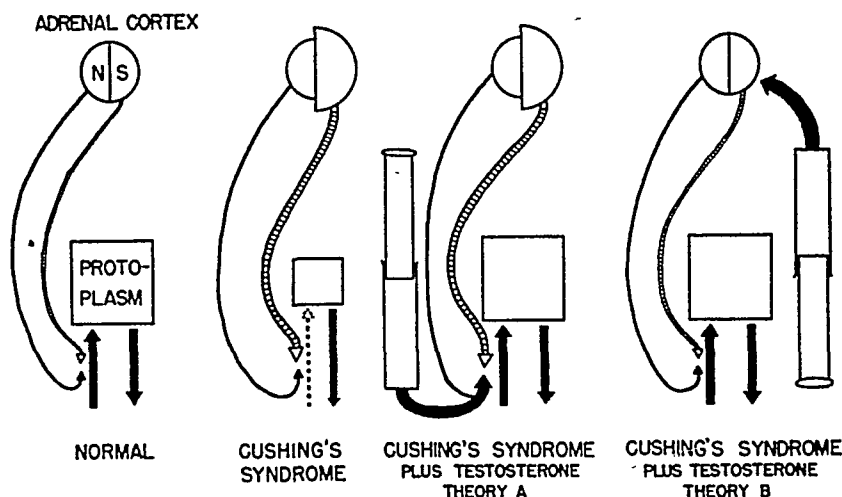


FIG. 13. Schematic diagrams to illustrate two of the possible actions of testosterone on protoplasm.

Note in the normal individual that protoplasm is being built up and broken down; that the adrenal cortical "N" hormone stimulates the anabolism of protoplasm and the adrenal cortical "S" hormone inhibits this action. Note in Cushing's syndrome that there is an excess of adrenal cortical "S" hormone and hence an inhibition of the anabolism of protoplasm. Note in Cushing's syndrome, when testosterone is administered by a syringe, that according to theory A it balances the inhibiting action of adrenal cortical "S" hormone and hence allows the normal anabolism of protoplasm; that according to theory B it inhibits production of adrenal cortical "S" hormone and hence allows the normal anabolism of protoplasm.

The above observations, by themselves, suggest that testosterone propionate affects protoplasm by inhibiting production of the anti-anabolic adrenal cortical "S" hormone. That this cannot be its only effect on protoplasm is shown by the fact that it causes nitrogen and phosphorus retention when administered to an individual devoid of adrenal cortical tissue—i.e. a patient with Addison's disease (figure 12). Thus, whether testosterone has a direct stimulating effect on anabolism of protoplasm, or whether it inhibits production of the antianabolic "S" hormone, or whether it does both these things, we must for the time being reserve judgment. In figure 13 are shown in schematic fashion the two manners in which testosterone may exert its effect on protoplasm.

*Stress-and-Strain Factor in Osteoporosis.* As mentioned above, the most fundamental stimulus for an osteoblast is the feeling on its part that the

skeleton is unstable. It follows that an osteoblast will stop producing if the skeleton is put at rest by being immobilized in a plaster cast<sup>7</sup> or by virtue of paralysis of the muscles pulling on the skeleton. This aspect of the subject is so self-evident that it is only mentioned here for completeness' sake. Osteoporosis from other causes often leads to a superimposed disuse atrophy which may be unavoidable, but which is often abetted by over-fixation on the part of the orthopedic surgeon. Disuse atrophy is also a factor in the osteoporosis of old age.

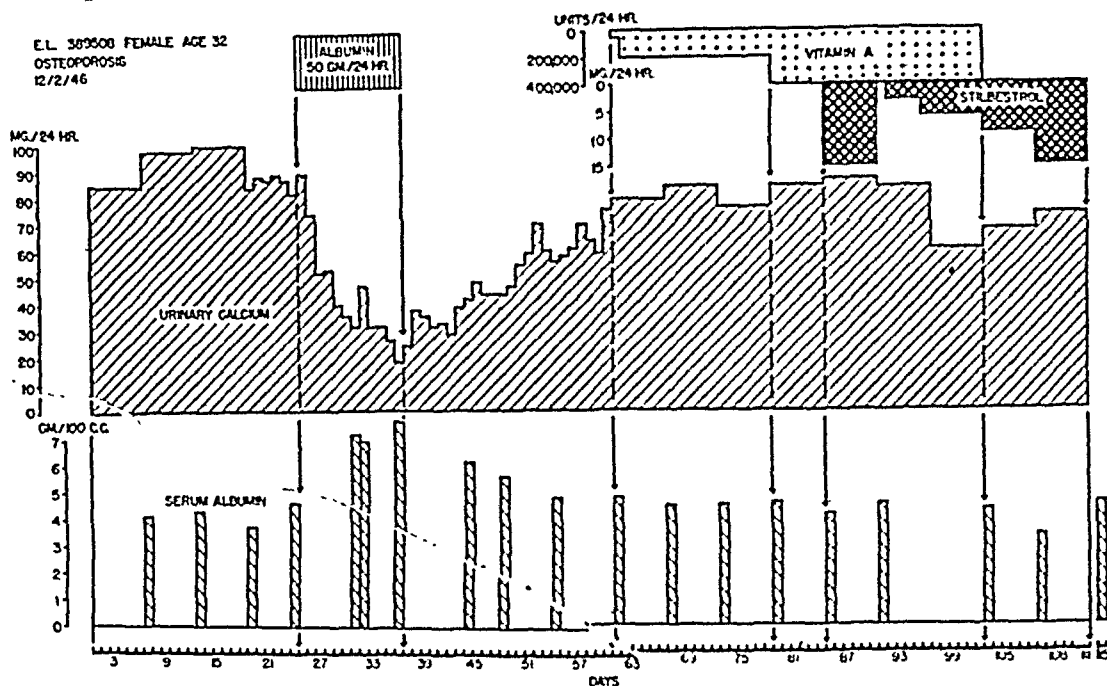


FIG. 14. Metabolic study on a patient with idiopathic osteoporosis to show the inverse relationship between the height of the serum albumin level and the urinary calcium excretion. Shown in the figure are 111 consecutive days during which the patient was on a constant dietary regimen. From day 25 through day 36 she received approximately 50 grams of purified serum albumin \* per day.

*Lack of Nitrogenous Building Blocks as a Cause of Osteoporosis.* It is obvious that the osteoblasts could be stimulated by a maximum of stresses and strains and by an optimal mixture of the anabolic steroids and still be incapable of producing bone matrix if the necessary nitrogenous building blocks were not available. Osteoporosis is a common finding in starvation and malnutrition. There is considerable circumstantial evidence that serum albumin may be one of the important building blocks. Severe osteoporosis is met in nephrosis.<sup>14</sup> We have studied two patients with idiopathic osteoporosis in whom the osteoporosis was made much worse by pregnancy, a condition in which the serum albumin is low; in one of these two patients a

\* The purified albumin preparation used in this study was made available to us by Dr. Edwin J. Cohn and Dr. Charles A. Janeway.

Note that vitamin A had no effect on the urinary calcium excretion and that diethylstilbestrol had a minimal effect, if any.

For further discussion, see text. This study will be published in detail elsewhere.<sup>14</sup>

therapeutic abortion was followed by a rise in the serum albumin level and a decrease in the negative calcium balance. With these observations in mind, we carried out a metabolic experiment with serum albumin on this same patient. The data are shown in figure 14. It will be seen that she received approximately 50 grams of purified serum albumin daily for 12 days while on a constant metabolic regimen. It will be noted that her urinary calcium excretion bore an inverse relationship to her serum albumin level. In a second experiment the same procedure was carried out except that the albumin was given by mouth rather than by vein; there was no fall in the urinary calcium excretion.

*It is concluded that serum albumin is one of the important nitrogenous precursors of bone matrix.*

### SUMMARY AND PRELIMINARY CONCLUSIONS

1. Osteoporosis is defined as that category of decreased bone mass where the disturbance is a failure of the osteoblasts to lay down bone matrix.

2. Three factors which influence osteoblastic activity are discussed: (a) steroidal hormones, (b) mechanical stresses and strains, and (c) nitrogenous building blocks.

3. In respect to bone matrix, the steroids can be divided into anabolic steroids (estrogens and androgens), anti-anabolic steroids (adrenal cortical "S" hormones), and anabolically-inert steroids (progesterone).

4. The age of entrance of adrenal cortical "N" hormone on the scene is termed the "adrenarche"; the age of exit, the "adrenopause." The adrenarche is usually synchronous with the menarche; the adrenopause is normally considerably later than the menopause. The adrenal cortical "S" hormone is produced at the same level during childhood, age of sexual maturity, and senility.

5. The osteoporosis of old age is partly to be attributed to the loss of gonadal hormones and of the adrenal-cortical "N" hormone and responds to estrogen and testosterone therapy.

6. The osteoporosis of the post-menopausal state is to be attributed to the decrease in estrogen production following the menopause and responds to estrin and testosterone therapy.

7. The osteoporosis in Cushing's syndrome and in the adaptation syndrome of Selye is to be attributed to an excess of the anti-anabolic adrenal cortical "S" hormone and responds to testosterone therapy.

8. The adrenocorticotrophic hormone, by releasing "S" hormone from the adrenal cortices, likewise produces osteoporosis; the effect of A.C.T.H. on panhypopituitarism is demonstrated.

9. Evidence is presented to suggest that the effect of testosterone in stimulating anabolism may be partly, but probably not wholly, due to its property of causing decreased production of the adrenal cortical antianabolic "S" hormone rather than entirely to a direct anabolic property of its own.



10. The production of bone matrix is undoubtedly influenced by the availability of certain nitrogenous substances; evidence is presented which suggests that the height of the serum albumin is an important factor.

### CONCLUDING REMARKS

1. I have told you more about osteoporosis than I know.
2. What I have told you is subject to change without notice.
3. I hope I have raised more questions than I have given answers.
4. In any case, as usual, a lot more work is necessary.

### BIBLIOGRAPHY

1. ALBRIGHT, F., SMITH, P. H., and RICHARDSON, A. M.: Post-menopausal osteoporosis: its clinical features, *Jr. Am. Med. Assoc.*, 1940, cxvi, 2465-2474.
2. ALBRIGHT, F.: Cushing's syndrome: its pathological physiology, its relationship to the adreno-genital syndrome, and its connection with the problem of the reaction of the body to injurious agents ("alarm reaction" of Selye), *The Harvey Lecture Series*, 1942-1943, xxxviii, 123-186.
3. ALBRIGHT, F., BURNETT, C. H., PARSON, W., REIFENSTEIN, E. C., JR., and ROOS, A.: Osteomalacia and late rickets: the various etiologies met in the United States with emphasis on that resulting from a specific form of renal acidosis, the therapeutic indications for each etiological sub-group, and the relationship between osteomalacia and Milkman's syndrome, *Medicine*, 1946, xxv, 399-479.
4. ALBRIGHT, F.: The effect of hormones on osteogenesis in man, *Recent Progress in Hormone Research: Proceedings of the Laurentian Conference*, 1947, i, 293-353.
5. REIFENSTEIN, E. C., JR., and ALBRIGHT, F.: The metabolic effects of steroid hormones in osteoporosis, *Jr. Clin. Invest.*, 1947, xxvi, 24-56.
6. REIFENSTEIN, E. C., JR., ALBRIGHT, F., and WELLS, S. L.: The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen, *Jr. Clin. Endocrinol.*, 1945, v, 367-395.
7. ALBRIGHT, F., BURNETT, C. H., COPE, O., and PARSON, W.: Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism, *Jr. Clin. Endocrinol.*, 1941, i, 711-716.
8. ALBRIGHT, F., SMITH, P. H., and FRASER, R.: A syndrome characterized by primary ovarian insufficiency and decreased stature: report of 11 cases with a digression on hormonal control of axillary and pubic hair, *Am. Jr. Med. Sci.*, 1942, cciv, 625-648.
9. SELYE, H.: The general adaptation syndrome and the diseases of adaptation, *Jr. Clin. Endocrinol.*, 1946, vi, 117-230.
10. TALBOT, N. B., SALTZMAN, A. H., WIXOM, R. L., and WOLFE, J. K.: The colorimetric assay of urinary corticosteroid-like substances, *Jr. Biol. Chem.*, 1945, clx, 535-546.
11. DEMPSEY, E. W.: Personal communication.
12. VENNING, E. H., and BROWNE, J. S. L.: Conference on Metabolic Aspects of Convalescence, Fourteenth Meeting, Nov. 12-13, 1946, New York, 186-187.
13. TALBOT, N. B., ALBRIGHT, F., SALTZMAN, A. H., ZYGMUNTOWICZ, A., and WIXOM, R.: The excretion of 11-oxycorticosteroid-like substances by normal and abnormal subjects (In press). *Jr. Clin. Endocrinol.*, 1947, vii, 331-350.
14. EMERSON, K., JR., and BECKMAN, W. W.: Calcium metabolism in nephrosis; I. a description of an abnormality in calcium metabolism in children with nephrosis, *Jr. Clin. Invest.*, 1945, xxiv, 564-572.
15. FORBES, A. P., ALBRIGHT, F., REIFENSTEIN, E. C., JR., BRYANT, D. F., COX, L. D., and DEMPSEY, E. F.: Studies on the fate of intravenously administered plasma protein (Submitted for publication).

## OBESITY \*

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ALTHOUGH the dangers and handicaps imposed by obesity have been enumerated by many writers, the seriousness of this disease is not fully appreciated. It is easy to shrug off "a few pounds of overweight" as something of little consequence, but in doing so the physician is ignoring what is perhaps his best chance to lengthen the life and diminish future illnesses of his patient. Statisticians have pointed out the increase in deaths from the degenerative diseases such as cancer, diabetes and heart disease,<sup>1</sup> and the implication has been that medicine is approaching a point of diminishing returns, that increasing efforts will reduce the death and illness rates only slightly. Actually, a great improvement in the health of the nation appears possible by means of the correction and prevention of obesity. Statistical studies have demonstrated the association of obesity with hypertension,<sup>2, 3</sup> pulmonary emphysema,<sup>4</sup> diabetes,<sup>5</sup> heart disease,<sup>2</sup> cancer,<sup>6</sup> acute and chronic nephritis,<sup>3, 7</sup> cirrhosis,<sup>7</sup> accidents<sup>7</sup> and atherosclerosis.<sup>8</sup>

These studies suggest that by the treatment of obesity the physician may ameliorate considerably the effects of many diseases for which otherwise he has little specific treatment. The increased dangers of surgical treatment<sup>9</sup> and pregnancy<sup>10</sup> in the presence of obesity, the greater severity of degenerative arthritis in the knees, hips and lumbar spine of the obese,<sup>11</sup> the increased incidence of gall-bladder disease<sup>9</sup> and the earlier appearance of varicose veins<sup>11</sup> are further reasons for the correction of obesity.

A statement which may impress the doubtful patient with the urgency for weight reduction is: "Between the ages of 45 and 55, 25 pounds of excess weight means a 25 per cent greater chance of dying within the next year; 50 pounds of overweight means that you have a 50 per cent greater chance of death in the next year than the person of normal weight."<sup>12</sup>

While there is no question but that obesity increases the incidence of a large number of pathologic processes, it cannot be assumed with such certainty that the reduction of the weight of an obese person to normal will give him health equivalent to that of the person who has never been obese. Some of the changes caused by obesity, such as emphysema,<sup>4</sup> tend to become irreversible in time, but others may be corrected by weight reduction.<sup>3</sup> It seems reasonable to assume that the shorter the duration and the less the degree of the obesity, the more easily will normal health expectancy be restored. It is, therefore, as important to prevent as to correct obesity.

\* Read at the meeting of the American College of Physicians, Chicago, Illinois, May 2, 1947.

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Aside from the reasons mentioned, there are serious psychologic problems stemming from obesity. Marked obesity is essentially a repulsive disease, and its victim tends to feel rejected, unable to join with others in many of the ordinary activities with complete acceptance. Because physical activity requires greater effort for the obese, the victim is likely to retreat to a state of inactivity and thereby perpetuate and accentuate the condition. The frequent occurrence of neuroses in the obese has been emphasized by several investigators.<sup>13-17</sup> It should be pointed out, however, that similar psychologic investigations of control groups of nonobese persons might have revealed a similar incidence and variety of neuroses. It is of course difficult to judge, also, what proportion of psychologic changes is the result of and how much is the cause for the obesity. Esthetic reasons for the treatment of obesity are not the least important. The desire to be attractive is possibly the most frequent reason that the overweight person goes to the physician for help in reduction of weight.

In consideration of all these factors, it would seem desirable that more doctors develop something of the missionary spirit and zeal in correcting obesity.

#### PHYSIOLOGY

Early in the investigations of obesity, several cases were reported in which there appeared to be a maintenance of obesity in spite of low caloric intakes.<sup>18, 19</sup> These findings seemed to confirm the popular idea that there are fat people who stay fat no matter how little they eat.<sup>20</sup> However, in more recent and better controlled studies it has been shown that obese persons must eat more than the average person in order to remain obese.<sup>18, 21-24</sup> This statement has been made previously in many forms and for emphasis it is here repeated: *Fat comes only from food, and obesity results only from eating more than is required to meet the energy requirements of the body.*<sup>25, 26</sup> There are many capable investigators, however, who believe that there are those with a tendency toward leanness who can overeat with impunity, and there are those with a predisposition to obesity who will become stout although eating no greater amount.<sup>20, 27</sup> It is felt by these investigators that some obese persons have an unusual mechanism for conserving energy not possessed by other people. It is sufficient to say that such a mechanism has never been adequately demonstrated,<sup>12, 23</sup> and the very multiplicity of suggested abnormalities of metabolism argues against such a possibility.

There are a number of devices which appear to regulate body weight. Perhaps the most important is the appetite mechanism. No one has been able to explain satisfactorily what determines satiation, but it probably depends upon the interaction of a number of factors.<sup>28</sup> The striking effect of hypothalamic damage in producing obesity through increased appetite<sup>29</sup> suggests that an important center for normal appetite regulation may reside

there. The importance of psychic conflict in the development of obesity in persons exhibiting compulsive eating has frequently been observed, thus demonstrating that the cerebral cortex may override the more automatic and primitive appetite control centers.

It is the familiar plaint of the fat person that "I don't eat a thing and I still get fat." It has been well proved that such a person does eat excessively,<sup>22, 24</sup> and it is interesting to speculate why this belief should so frequently arise. A possible explanation is that the person with the predisposition to obesity has an appetite mechanism (whatever that may consist of) which requires a larger than normal amount of food before satiation is accomplished. If he eats what would satisfy the normal person he remains hungry and feels that he has eaten very little; if he eats anything less than what is required for satiation he is likely to believe honestly that he has eaten little, even though he has consumed large quantities of food. A corresponding situation appears to exist for the person with a tendency toward leanness.

Another device for regulation of body weight is the association of energy requirement with the surface area.<sup>22, 23, 25, 30</sup> It has been shown that the number of calories required by the body at resting state is proportional to the surface area. Thus a 35 year old man, 5 feet and 7 inches (170 cm.) tall with a surface area of 1.79 square meters will maintain a normal weight of 150 pounds (68 kg.) with an intake of 2,415 calories each 24 hours (table 1).

TABLE I  
Varying Food Requirements for a 35 Year Old Man at Different Body Weights \*

Weight, Pounds	Surface Area, Square Meters	Calories Required per 24 Hours	
		At Basal Conditions	With Moderate Activity†
100	1.50	1,360	2,040
150	1.79	1,610	2,415
200	2.02	1,840	2,760
250	2.22	2,020	3,030
300	2.40	2,170	3,255

\* These calculations assume a basal metabolic rate of 0 and were obtained by use of the Boothby-Berkson nomogram for a 35 year old man 5 feet and 7 inches tall who had a standard weight of 150 pounds.

† Caloric requirements at moderate activity are assumed to be 50 per cent greater than those at basal conditions.

If he consumes 3,255 calories (34 per cent more) he will gradually gain in weight until he reaches 300 pounds (136 kg.) and a surface area of 2.4 square meters (34 per cent greater). The weight gain of such a man weighing 150 pounds and eating 3,255 calories will at first be 1.7 pounds (0.8 kg.) per week. The rate of gain will gradually become slower until it ceases at 300 pounds. Similarly if this same man weighed 300 pounds and were fed 2,415 calories daily he would lose 1.7 pounds a week at first, the rate of loss gradually slowing as his weight approached 150 pounds. From

these figures \* it can be seen that a small daily excess of food does not lead to unlimited gains in weight as once postulated by von Noorden,<sup>19</sup> but rather to definite, calculable and limited increases. This removes some of the mystery with which the appetite mechanism was surrounded when von Noorden pictured it as a device of almost incredible accuracy. It also diminishes the necessity for postulating obscure aberrations in energy metabolism which would adjust energy output to fit the intake.

Another phenomenon which aids in the regulating of weight is the fall in the basal metabolic rate with decreased intake of food. After several weeks on a reduced diet, there is often, but not invariably<sup>16, 32</sup> a decrease in the basal metabolic rate. This phenomenon is less pronounced in the obese (as if there were less necessity for conserving their stores of fat) but amounts to a considerable saving in energy output in the starving person who begins at a normal weight.<sup>25, 33</sup> The converse, that excessive eating might increase the basal metabolic rate, does not appear to be an important factor in the regulation of weight.<sup>31</sup> The basal metabolic rate in obese persons is characterized by approximately the same range of variability as in those of normal weight, the rates for the overwhelming majority falling within normal limits.<sup>30</sup> This normality is misleading, however, as shown by Strang and Evans.<sup>33</sup> The heart, liver and other viscera are providing for the production of 1,610 calories per 24 hours at basal conditions in our man of 150 pounds but when he gains to 300 pounds those same viscera are maintaining an organism which produces 2,170 calories, an increase of 34 per cent (table 1).

### ETIOLOGY

The concept of endogenous and exogenous obesity was championed early in the century by von Noorden,<sup>35</sup> and it has remained popular since. Newburgh<sup>23</sup> has expressed the feeling that the distinction is unimportant and that all obesity is exogenous since all fat is derived from the consumption of food in excess of requirements and because there have been no well controlled cases in which there was failure to lose weight on a sufficiently restricted diet. On the other hand it has been argued that all obesity is endogenous since the factors which initiate the overeating, such as psychologic conflicts or hypothalamic damage, originate within the person.<sup>36</sup> It would seem wisest to abandon the terms "endogenous" and "exogenous."<sup>37</sup>

The etiology of obesity will be discussed under a number of headings in this paper, but the outline should not be taken as a classification of obesity. Rather it should be considered as a list of mechanisms which have been proposed, of which only a few have been accepted as of any importance.

*Hypothalamic Damage.* Injury to the hypothalamus has been shown to interfere with a variety of self-regulatory functions such as temperature control and water balance. Injury to the paraventricular nuclei in the posterior portion of the hypothalamus causes obesity which results prin-

\* Calculations were made by means of the Boothby-Berkson nomogram<sup>31</sup> and the factor for predicting weight loss given by Wilder.<sup>26</sup>

cipally from a great increase in appetite beginning abruptly after the damaging procedure.<sup>29, 38</sup> Hypothalamic changes rather than the originally presumed pituitary damage are now thought to have been responsible for the obesity observed by Fröhlich in his famous case reported in 1904.<sup>39</sup> Since pituitary damage alone seems to cause no pronounced constant change in weight,<sup>29</sup> and because the term "Fröhlich's syndrome" has been used frequently to describe the child or adolescent whose genitalia are partly obscured by masses of adipose tissue, it would seem desirable to abandon this term.<sup>39</sup>

Soon after the epidemic of encephalitis which occurred in 1918 a variety of symptoms began to appear in its victims.<sup>40, 41</sup> Among other manifestations of the postencephalitic syndrome there was obesity, and there is good evidence to believe that this was a result of damage to the hypothalamus which in turn increased the intake of food.

*Injury to the Cerebral Cortex.* The possibility that tumors of the frontal lobe may cause obesity has been discussed but the evidence is not convincing.<sup>13</sup>

*Psychologic Factors.* As the phylogenetic scale is ascended the cerebral cortex exerts an ever greater modifying influence on the functions of the lower nervous centers. As the individual matures, the cortex also assumes a greater control over such basic functions as eating, sleeping and procreation. There can be no argument but that our civilization has modified all such functions tremendously, and the aspect that each presents in various cultures is chiefly a mirror of that culture. Eating has acquired a considerable social significance in our own social order, not only in the nature and time of meals but in the amount eaten.<sup>14, 42</sup>

While it is true that most infants and children have less modification of their hypothalamic impulses by the cerebral cortex than do adults, yet Bruch<sup>14, 43</sup> has shown in a series of fundamental articles that obesity of psychologic origin can begin early in childhood. The mothers of such children would go to extremes in protecting their children from even the minor conflicts of living but paradoxically would entertain great ambitions for them. These children would be prevented from playing with other children and would be bathed and dressed by their mothers far beyond the usual age for such care. Within families containing obese children there is frequently a great emphasis on food. Desserts and candies are used as rewards for good behavior; conversation centers around delicacies of the table; and the child gains the feeling that food is the end and purpose of life. The mothers of obese children were found by Bruch<sup>14</sup> to be starved emotionally, disappointed in their husbands, worried over domestic strife and often disappointed in the sex of their children. As if in compensation these mothers attempt to pour out a love to their children that they do not honestly feel. In such an attempt they give the most obvious things, food, protection from the unpleasantness of work and contact with other children "who might play rough"; still these mothers are unable to give their children true affection. Similar situations undoubtedly occur in the lives of the lean, however.

Such a situation acting upon a child can lead to obesity in a number of ways. The protection from rough play and exertion diminishes the amount of energy expended. The atmosphere of gormandizing and the continual urging to eat will increase the amount of food eaten. Furthermore, the emotional starvation of the child who perceives the real emptiness of his mother's show of affection may lead to a compensatory increase in food consumption as though the child were trying to satisfy his emotional hunger by the eating of food.

While these factors have been repeatedly demonstrated by several observers, it may properly be asked whether similar factors do not frequently occur without the development of obesity. This view finds some confirmation in the investigations in the etiology of anorexia nervosa.<sup>44</sup> Here is a syndrome, almost invariably a manifestation of an emotional conflict, which has many close similarities to obesity while superficially completely different. Both are disorders of the mechanism which regulates the quantity of food intake. Frequently anorexia nervosa is preceded by obesity or the two conditions may alternate.<sup>44</sup> Both are more frequent in women than in men and both respond most dramatically to proper diet and psychotherapy. This response to diet and psychologic treatment alone is dramatic when contrasted with the numerous articles urging the use of endocrine substances and giving support to endocrinologic theories of causation of the two conditions.

The emotional factors which led to obesity initially should not cause the physician to overlook the conflicts which result from obesity and tend to perpetuate it. The obesity itself becomes a handicap which prevents the patient from obtaining exercise. This in turn diminishes energy output and causes further weight gain. The obesity is sometimes unconsciously used by the patient as a means of protection against doing unpleasant things. Obesity may repel suitors and protect the obese girl from the responsibilities of marriage. It may play a part in the selection of an occupation, preventing the obese person from doing difficult work.<sup>17</sup> The feeling of being set apart from other people because of the physical disfigurement of obesity tends to cause a certain amount of emotional starvation which perpetuates the increased appetite. Not only must the physician overcome the factors which initiated the weight gain but he must solve those which have arisen as a result of the obesity.

*Endocrine Factors.* One of the most regrettable practices in medicine is the attempt to diagnose numerous endocrinologic aberrations by means of slight variations in distribution of body fat.<sup>45, 46</sup> These elaborate classifications into types have little or no basis in controlled investigation and are usually misleading.<sup>27, 47</sup>

*Pituitary body.* No definite pituitary obesity has been proved. Cushing's disease now seems to be associated more closely with the adrenal cortex. The posterior lobe of the pituitary has been implicated because some have expressed the belief that an excess of the antidiuretic hormone may cause obesity by retention of water.<sup>48</sup> We are acquainted with no experimental

studies which have produced obesity in animals or human beings by the injection of pituitrin, a simple proof if this theory had any basis in fact. Recent experiments have suggested that the pituitary gland may regulate fat deposition through the lactogenic hormone.<sup>49</sup> This awaits confirmation.

Thyroid gland. In myxedema and hypothyroidism without myxedema, there is no increased incidence of obesity.<sup>50, 51</sup>

Adrenal glands. Hyperfunction of the adrenal cortex may result in Cushing's syndrome. In this condition there is frequently an increase in the total amount and always a characteristic distribution of the adipose tissue. Restriction of diet in Cushing's syndrome will cause loss of weight as in any other obese person.<sup>12, 23</sup>

Pancreas. True hyperinsulinism (that due to a functioning islet cell tumor) appears to cause obesity by means of an increased appetite which depends upon pronounced hypoglycemia.<sup>52</sup> It has been shown in animals that increased appetite results during insulin therapy only if the hypoglycemia approaches shock levels.<sup>53</sup> Obesity is mentioned as a symptom of the functional hypoglycemia described by Rennie and Howard,<sup>54</sup> but not of that reported by Alexander and Portis.<sup>55</sup> In well-developed obesity, hyperglycemia rather than hypoglycemia is considered characteristic.<sup>23</sup> Therefore it seems probable that hypoglycemia plays an unimportant part in the production of obesity.

Gonads. There is no definite proof that the gonads have significant effect upon the amount of fat in man,<sup>27, 47</sup> although they may influence its distribution. This contrasts with the effect in animals in which castration is frequently used as a means of increasing the deposition of fat.

Pineal body. The evidence is inconclusive that the pineal body has any influence on fat deposition.<sup>56</sup>

*Genetic Factors.* The Laurence-Moon-Biedl syndrome consists of mental deficiency, retinitis pigmentosa, hypogenitalism, obesity and polydactyly and appears to be inherited in a recessive manner.<sup>57</sup> The Morgagni-Stewart-Morel syndrome is perhaps better called "hyperostosis frontalis interna" and is inherited in a dominant manner.<sup>58</sup> It is manifested almost invariably by internal hyperostosis of the frontal bone and headache; frequently by obesity, impotence, amenorrhea, benign hypertensive cardiovascular disease, hirsutism, psychosis of indefinite nature or psychoneurosis, fatigability and weakness; and sometimes by disturbances in olfaction, Bell's palsy, diplopia and amblyopia. Headache is so constant that this diagnosis should be considered in all patients complaining of cephalalgia.<sup>58</sup> In neither of these disorders is there good evidence of endocrine dysfunction or of a disturbed fat metabolism which might cause obesity.

Gurney<sup>59</sup> found that obesity is much more frequent in some families than in others. Experiments with the yellow mouse have demonstrated a form of obesity which is inherited in a Mendelian manner.<sup>60</sup> However, it remains to be demonstrated whether the gene or environment is the more important factor in human obesity. While at present we cannot state definitely the



importance of heredity in obesity, we can emphasize to the patient with fat parents that he will respond to treatment in exactly the same way as will a person with parents of normal weight. Such a patient should be told that fat is just as dangerous to him as to anyone else and that the fact that his parents were fat cannot be used as an excuse to avoid the necessary corrective measures.

*Constitutional Abnormality of the Adipose Tissue.* An abnormal avidity of the adipose tissue of the person "predestined" to be obese has been postulated and named "lipophilia."<sup>61</sup> No proof of this exists.<sup>12, 62</sup> An entity known as "progressive lipodystrophy" characterized by wasting above the waist and obesity below is poorly understood<sup>63</sup> and the emaciation appears to be the significant pathologic aspect of this condition.

Dercum's disease, or adiposis dolorosa, is a syndrome consisting of tender and painful fat nodules in a patient partly disabled by weakness and psychoneurotic symptoms.<sup>63</sup> It has not been established as an entity and nothing of certainty is known of any cause or pathologic physiology.

*Disorders in the Use of Energy.* Excessive gastrointestinal absorption. This has been disproved in experiments which show that obese and normal persons absorb the same proportion of calories, nitrogen and fat from their diet.<sup>23, 62</sup>

Static obesity. Obesity due to inactivity and a diminished output of energy means that the appetite mechanism has failed to adjust the appetite to the energy requirements.<sup>15</sup>

Increased efficiency of the obese in doing work. Actually the obese person has a decreased mechanical efficiency and expends extra energy in doing the same amount of work.<sup>32, 64</sup>

Abnormal respiratory quotients. The respiratory quotient and its vagaries have been intensely studied for clues to the cause of obesity but no significant deviations have been found.<sup>30</sup>

Reduced specific dynamic action. This abnormality has not been demonstrated in obesity when the specific dynamic action is calculated properly.<sup>65</sup>

Negative phase of metabolism. Bernhardt<sup>66</sup> thought he had discovered a lowering of the metabolic rate to less than the basal rate after exercise or eating which was peculiar to the obese and effected an economy of energy which explained the development of obesity. This hypothesis was disproved by Wilder.<sup>64</sup>

Luxuskonsumption. This was a device postulated by Grafe and Graham<sup>67</sup> to explain why the normal person did not get fat. The normal person was thought to undergo an acceleration of metabolism after eating which consumed excess food. An absence of this phenomenon was suggested as an explanation for obesity. This theory was disproved by Wiley and Newburgh.<sup>34</sup>

Ketosis. Ketosis in fasting obese patients has been studied for clues to the origin of obesity, but no consistent abnormalities have been found.<sup>68</sup>

*Water Retention.* Water retention has been suggested as a primary

cause of obesity.<sup>45, 48</sup> In the absence of pitting edema it is doubtful whether any large accumulation of weight could take place from water retention alone.

### TREATMENT

There are no absolute contraindications to reduction of weight. A number of conditions in which reduction had best be done slowly and perhaps only when the patient is grossly obese are active or recently active tuberculosis, active peptic ulcer, gout, cirrhosis, Addison's disease and chronic ulcerative colitis. All of these conditions, except gout and peptic ulcer, tend to cause loss of weight so that the incidence of obesity in patients who have such diseases is low. It should be remembered that a properly devised reduction diet is often more nearly ideal for the therapy of the patient's condition than is the diet which is unrestricted in calories and which is selected by the patient himself after a few general directions given by the doctor.

One should be particularly certain that all essential foods are present in diets of children and pregnant women. Old age, hypertension and coronary artery disease are certainly no bars to reduction but rather are urgent reasons for it.

*Diet.* This is the most important measure in weight reduction. There is fairly good agreement that a reduction diet should contain an adequate supply of protein (1 gm. or more for each kilogram of body weight), a minimum of fat and enough carbohydrate to prevent wasting of protein. Such a diet permits the loss of large quantities of adipose tissue with little or no wasting of the protein structures of the body. Multiple vitamin supplements are advisable. It is advisable to add sufficient skimmed milk to the diet so that the patient does not require added calcium which, in the forms ordinarily prescribed, are poorly absorbed. The caloric content of the diet should be low enough to insure a definite weight loss and high enough to permit the inclusion of essential food materials. Such diets will provide a range between 600 and 1,500 calories and the selection of the diet should depend upon the physician's estimate of the situation. Space prevents publication of diet lists in this article, but representative diets may be found in the following references<sup>12, 25, 26</sup> and in a monograph by Rynearson and Gastineau now in press.

It is encouraging to the patient to be told that he will lose a definite amount each week. This can be calculated in the following manner:

1. Determine the caloric requirement for 24 hours at basal conditions by means of the Boothby-Berkson nomogram,<sup>31</sup> which is available in Wilder's primer for diabetics. Use the patient's actual height and assume a weight 30 pounds less than his actual weight in employing the nomogram.

2. Add 50 per cent.

3. Subtract the caloric value of the reduction diet selected.

4. Multiply by 0.002. The result obtained is the weight in pounds which will be lost in one week.<sup>26</sup>

Psychotherapy. Under this term can be placed the impression the personality and attitudes of the physician make upon the patient. Under this term can also be included all of those nebulous psychologic factors that make up the doctor-patient relationship. The physician who by his manner inspires confidence and a desire to follow his orders is most likely to succeed.

Ross<sup>69</sup> has shown quite well how the physician completely convinced of the efficacy of a certain treatment will by his manner transmit that conviction to the patient. If there is a large psychologic element in the illness concerned, then a remarkable improvement follows and the physician is further impressed by the worth of his therapy. A similar phenomenon may occur in the treatment of obesity. The doctor who believes he has found an endocrine or other type of preparation that will cure obesity will have the patient return to his office at frequent intervals for injections. The patient, impressed by the doctor's enthusiasm for his drug, becomes hopeful for success and anxious to aid in every way possible. Under such circumstances it is not surprising that the diet instructions are followed more closely and a good result is obtained. Thus the physician is further convinced of the efficacy of his drug. It is only when the doubting physician uses the drug that it fails.

A disadvantage to the use of any medication is that the patient may decide that the medication is the important factor in therapy and that a few violations of the diet will be of no consequence. Therefore we feel that it is best in most instances to tell the patient that his fat comes from eating too much and that reduction of the amount of food is the only way to reduce his excess weight. Most patients appreciate the honesty of this approach and will cooperate.

Superficial psychotherapy in the form of encouragement and reassurance may be sufficient in the majority of cases, but often the internist will find himself listening to the story of a profound neurosis and occasionally may be forced to refer such a patient to a trained psychiatrist.

*Drugs.* Thyroid speeds the metabolism, causes a negative nitrogen balance,<sup>70</sup> exerts a direct toxic action on the heart<sup>71</sup> and has long been used for the treatment of obesity. It is probable that small doses (1 to 2 grains [0.065 to 0.13 gm.] daily) of thyroid are inactivated<sup>72</sup>; larger doses may cause undesirable loss of body protein and an increased strain on a cardiovascular system already overburdened with an obesity-accelerated metabolism.<sup>25, 33</sup>

For these reasons it seems unreasonable to urge the use of thyroid, although many physicians find its use to be without harm when the patient is followed carefully and occasional determinations of the basal metabolic rate are made.

Other endocrine preparations have been used without effect in obesity. A few of these have been posterior and anterior pituitary extracts, ovarian extracts and estrogens.

Amphetamine and other sympathomimetic amines<sup>15</sup> have been used as

metabolic stimulants and as depressors of the appetite mechanism. It is probable that sufficiently large doses will cause a true depression of the appetite,<sup>73, 74</sup> but it is also likely that an elevation in basal metabolic rate and blood pressure lasting for several hours will follow.<sup>75</sup> Because this effect probably will not be detected if the basal metabolic rate is determined in the morning 12 or 15 hours after the last administration of the drug, many authors report that amphetamine has no effect on basal metabolic rate.

These amines share with all other medications the fault that they divert the patient's attention from the diet, the most important factor.<sup>16</sup> The use of amphetamine in obesity, within such limits as may be necessary to produce a reduction of appetite of the individual, has been approved by the Council on Pharmacy and Chemistry of the American Medical Association.<sup>76</sup>

In all fairness it should be added that many physicians are more enthusiastic regarding the use of these drugs than are we and they may be correct. More controlled observations are necessary before conclusions are reached.

Dinitrophenol is ineffective without diet limitation and its toxic reactions have caused its use to be stopped.<sup>77</sup>

Belladonna has been used<sup>35, 78</sup> but the results are not conclusive.

Diuretics may give the physician and patient a false sense of achievement by causing the excretion of a few pounds of water.<sup>48</sup>

*Salt Restriction and Heat Treatments Which Encourage Perspiration.* These are effective in much the same manner as diuretics. They are of no real value, all weight loss by their agency representing only water.

*Exercise and Massage.* These have no effect on local deposits of fat.<sup>79, 80</sup> Exercise is a relatively ineffective means of using energy and vigorous exercise is not wise in most obese patients.<sup>23</sup>

*Surgical Measures.* Procedures by which large amounts of fat have been removed have not proved practical.

## SUMMARY

Obesity is one of the most pressing and dangerous health problems we face today. Much can be accomplished to improve the health of the general population by a vigorous effort to encourage the obese to reduce.

The development of obesity seems most frequently to depend upon a derangement of the appetite control mechanism. Circumstantial evidence suggests that this mechanism may reside within the hypothalamus and that its functions may be considerably modified by the cerebral cortex. Obesity may result from the inheritance of an appetite control center which demands more food for satiation. On the other hand, the important factor of environment cannot be ignored. Cerebral cortical function in the form of neuroses may modify the more automatic appetite control mechanisms.

A few unusual forms of obesity are recognized. The postencephalitic form results from injury to the hypothalamus. The Laurence-Moon-Biedl and the Morgagni-Stewart-Morel syndromes are rare conditions depending upon heredity.

Many other causes of obesity have been suggested but no good evidence exists for other than those already listed.

No abnormal metabolism has been demonstrated in obesity.

Therapy depends upon the limitation of caloric intake. Endocrine products and diuretics are neither necessary nor desirable parts of the reduction program.

Physicians are not unanimous in approving the use of thyroid extracts or stimulating drugs such as amphetamine. Most physicians do agree that the patient's attention should not be diverted from the diet as the fundamental basis for treatment.

#### BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 1944, Ed. 3, The Macmillan Company, New York, 1,025 pp.
2. LEVY, R. L., WHITE, P. D., STROUD, W. D., and HILLMAN, C. C.: Overweight; its prognostic significance in relation to hypertension and cardiovascular-renal diseases, Jr. Am. Med. Assoc., 1946, cxxxi, 951-953.
3. LEY, H. A., JR.: The effect of change in weight on blood pressures as shown in a study of 3,516 examinees, Proc. Life Ext. Exam., 1939, i, 33-36.
4. KERR, W. J., and LAGEN, J. B.: The postural syndrome related to obesity leading to postural emphysema and cardiorespiratory failure, Ann. Int. Med., 1936, x, 569-595.
5. JOSLIN, E. P., DUBLIN, L. I., and MARKS, H. H.: Studies in diabetes mellitus. III. Interpretation of the variations in diabetes incidence, Am. Jr. Med. Sci., 1935, clxxxix, 163-192.
6. TANNENBAUM, ALBERT: Relationship of body weight to cancer incidence, Arch. Path., 1940, xxx, 509-517.
7. DUBLIN, L. I.: Influence of weight on certain causes of death, Human Biol., 1930, ii, 159-184.
8. WILENS, S. L.: Bearing of general nutritional state on atherosclerosis, Arch. Int. Med., 1947, lxxix, 129-147.
9. FAUST, R. A.: Complications of obesity, New Orleans Med. and Surg. Jr., 1946, xcvi, 502-507.
10. ODELL, L. D., and MENGERT, W. F.: The overweight obstetric patient, Jr. Am. Med. Assoc., 1945, cxxviii, 87-89.
11. DANOWSKI, T. S., and WINKLER, A. W.: Obesity as a clinical problem, Am. Jr. Med. Sci., 1944, ccviii, 622-630.
12. NEWBURGH, L. H.: Obesity, Arch. Int. Med., 1942, lxx, 1033-1096.
13. BRUCH, HILDE: Obesity in childhood. III. Physiologic and psychologic aspects of the food intake of obese children, Am. Jr. Dis. Child., 1940, lix, 739-781.
14. BRUCH, HILDE, and TOURAINE, GRACE: Obesity in childhood: V. The family frame of obese children, Psychosom. Med., 1940, ii, 141-206.
15. FREED, S. C.: Psychic factors in the development and treatment of obesity, Jr. Am. Med. Assoc., 1947, cxxxiii, 369-373.
16. NICHOLSON, W. M.: Emotional factors in obesity, Am. Jr. Med. Sci., 1946, ccxii, 443-447.
17. RENNIE, T. A. C.: Obesity as manifestation of personality disturbance, Dis. Nerv. System, 1940, i, 238-247.
18. MØLLER, EGGERT: Results of exclusively dietary treatment in 46 cases of obesity, Acta med. Scandinav., 1931, lxxiv, 341-352.
19. VON NOORDEN, CARL: Metabolism and practical medicine, 1907, W. T. Keener & Company, Chicago, vols. 1, 2 and 3, 452 pp., 525 pp., and 1,320 pp.
20. STROUSE, SOLOMON, and DYE, M.: Studies on the metabolism of obesity. I. The relation between food intake and body weight in some obese persons, Arch. Int. Med., 1924, xxxiv, 267-274.

21. CONN, J. W.: Obesity. II. Etiological aspects, *Physiol. Rev.*, 1944, xxiv, 31-45.
22. NEWBURGH, L. H.: The cause of obesity, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1659-1663.
23. NEWBURGH, L. H.: Obesity. I. Energy metabolism, *Physiol. Rev.*, 1944, xxiv, 18-31.
24. STRANG, J. M., McCLUGAGE, H. B., and EVANS, F. A.: Further studies in the dietary correction of obesity, *Am. Jr. Med. Sci.*, 1930, clxxix, 687-694.
25. EVANS, F. A.: Obesity. In DUNCAN, G. G.: Diseases of metabolism; detailed methods of diagnosis and treatment, 1942, W. B. Saunders Company, Philadelphia, chap. 10, pp. 513-591.
26. RYNEARSON, E. H., and SPRAGUE, ANNE W.: Obesity, *California and West. Med.*, 1940, ciii, 158-162.
27. GREENE, RAYMOND: Adiposity, *Post-Grad. Med. Jr.*, 1946, xxii, 169-181.
28. CHENEY, GARNETT: Hunger and appetite; present conceptions in regard thereto, *California and West. Med.*, 1929, xxx, 145-150.
29. BROBECK, J. R.: Mechanism of the development of obesity in animals with hypothalamic lesions, *Physiol. Rev.*, 1946, xxvi, 541-559.
30. DU BOIS, E. F.: Basal metabolism in health and disease, 1936, Ed. 3, Lea & Febiger, Philadelphia, 494 pp.
31. WILDER, R. M.: A primer for diabetic patients, 1946, Ed. 8, W. B. Saunders Company, Philadelphia, 192 pp.
32. WANG, C. C., STROUSE, SOLOMON, and MORTON, ZELMA O.: The metabolism of obesity. V. Mechanical efficiency, *Arch. Int. Med.*, 1930, xlv, 727-733.
33. STRANG, J. M., and EVANS, F. A.: The energy exchange in obesity, *Jr. Clin. Invest.*, 1938, vi, 277-289.
34. WILEY, F. H., and NEWBURGH, L. H.: The doubtful nature of "Luxuskonsumption," *Jr. Clin. Invest.*, 1931, x, 733-744.
35. GREENE, J. A.: The effect of belladonna on the appetite of patients with obesity and with other diseases, *Jr. Lab. and Clin. Med.*, 1940, xxvi, 477-478.
36. SILVER, SOLOMON, and BAUER, JULIUS: Obesity, constitutional or endocrine? *Am. Jr. Med. Sci.*, 1931, clxxxi, 769-777.
37. RYNEARSON, E. H., and HILDEBRAND, ALICE G.: Metabolism and diabetes; review of certain recent contributions, *Arch. Int. Med.*, 1941, lxxviii, 134-175.
38. HEINBECKER, PETER, WHITE, H. L., and ROLF, DORIS: Experimental obesity in the dog, *Am. Jr. Physiol.*, 1944, cxli, 549-565.
39. BRUCH, HILDE: The Fröhlich syndrome; report of the original case, *Am. Jr. Dis. Child.*, 1939, lviii, 1282-1289.
40. EAVES, ELIZABETH C., and CROLL, MARGARET M.: The pituitary and hypothalamic region in chronic epidemic encephalitis, *Brain*, 1930, liii, 56-75.
41. WALSH, T. G.: Postencephalitic obesity; report of cases, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 305-307.
42. HOCHMAN, SAMUEL: Mental and psychological factors in obesity, *Med. Rec.*, 1938, cxlviii, 108-111.
43. BRUCH, HILDE: Obesity in childhood. I. Physical growth and development of obese children, *Am. Jr. Dis. Child.*, 1939, lviii, 457-484.
44. WALLER, J. V., KAUFMAN, M. R., and DEUTSCH, FELIX: Anorexia nervosa: a psychosomatic entity, *Psychosom. Med.*, 1940, ii, 3-16.
45. GOLDZIEHER, M. A.: Endocrine aspect of obesity, *Am. Jr. Digest. Dis.*, 1946, xiii, 40-54.
46. JARLØV, EJNAR: The clinical types of abnormal obesity, *Acta med. Scandinav.*, 1932 (Suppl.), xlii, 1-70.
47. GREENHILL, J. P.: Office gynecology, 1940, Ed. 3, The Year Book Publishers, Inc., Chicago, 424 pp.
48. ROWNTREE, L. G., and BRUNSTING, L. A.: Water or fat? Water retention in so-called endocrine obesity, *Endocrinology*, 1933, xvii, 377-382.
49. REISS, MAX: Lactogenic hormone and fat metabolism, *Endocrinology*, 1947, xl, 294-298.

50. MACKAY, E. M., and SHERRILL, J. W.: Influence of thyroidectomy on fat deposition in the rat, *Endocrinology*, 1941, xxviii, 518.
51. PLUMMER, W. A.: Body weight in spontaneous myxedema, *Trans. Am. Assoc. Study Goiter*, 1940, pp. 88-97.
52. WHIPPLE, A. O.: Present-day surgery of the pancreas, *New England Jr. Med.*, 1942, ccxxvi, 515-526.
53. BARNES, B. O., and KEETON, R. W.: Experimental obesity, *Am. Jr. Physiol.*, 1940, cxxix, 305-306.
54. REÑNIE, T. A. C., and HOWARD, J. E.: Hypoglycemia and tension-depression, *Psychosom. Med.*, 1942, iv, 273-282.
55. ALEXANDER, FRANZ, and PORTIS, S. A.: A psychosomatic study of hypoglycaemic fatigue, *Psychosom. Med.*, 1944, vi, 191-206.
56. BING, J. F., GLOBUS, J. H., and SIMON, H.: Pubertas praecox: survey of reported cases and verified anatomical findings, with particular reference to tumors of pineal body, *Jr. Mt. Sinai Hosp.*, 1938, iv, 935-965.
57. JENKINS, R. L., and PONCHER, H. G.: Pathogenesis of the Laurence-Biedl syndrome, *Am. Jr. Dis. Child.*, 1935, i, 178-186.
58. KNIES, P. T., and LE FEVER, H. E.: Metabolic craniopathy: hyperostosis frontalis interna, *Ann. Int. Med.*, 1941, xiv, 1858-1892.
59. GURNEY, R.: The hereditary factor in obesity, *Arch. Int. Med.*, 1936, lvii, 557-561.
60. DANFORTH, C. H.: Hereditary adiposity in mice, *Jr. Hered.*, 1927, xviii, 153-162.
61. BERGMANN: Das Problem der Herabsetzung des Umsatzes bei der Fettsucht, *Deutsch. med. Wchnschr.*, 1909, xxxv, 611-613.
62. WILDER, R. M., and WILBUR, D. L.: Diseases of metabolism and nutrition; review of certain recent contributions, *Arch. Int. Med.*, 1938, lxi, 297-365.
63. HOFFMAN, JACOB: Female endocrinology including sections on the male, 1944, W. B. Saunders Company, Philadelphia, 788 pp.
64. WILDER, R. M., SMITH, FLORENCE H., and SANDIFORD, IRENE: Observations on obesity, *Ann. Int. Med.*, 1932, vi, 724-742.
65. STRANG, J. M., and MCCLUGAGE, H. B.: The specific dynamic action of food in abnormal states of nutrition, *Am. Jr. Med. Sci.*, 1931, clxxxii, 49-81.
66. BERNHARDT, HERMANN: New concepts concerning the pathogenesis of obesity and the problems of basal metabolism, *Endocrinology*, 1930, xiv, 209-225.
67. GRAFE, E., and GRAHAM, D.: Über die Anpassungsfähigkeit des tierischen Organismus an überreichliche Nahrungsszufuhr, *Ztschr. f. physiol. Chem.*, 1911, lxxiii, 1-67.
68. RONY, H. R.: Obesity and leanness, 1940, Lea & Febiger, Philadelphia, 300 pp.
69. ROSS, T. A.: The common neuroses, their treatment by psychotherapy; an introduction to psychological treatment for students and practitioners, 1937, Ed. 2, William Wood & Company, Baltimore, 236 pp.
70. BOOTHBY, W. M., SANDIFORD, IRENE, SANDIFORD, KATHLEEN, and SLOSSE, JEAN: The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. I. A method of studying the reserve or deposit protein with a preliminary report of the results obtained, *Trans. Assoc. Am. Phys.*, 1925, xl, 195-228.
71. RASMUSSEN, HÅKON: Influence of the thyroid hormone on heart and circulation; experimental investigations in dogs, *Acta med. Scandinav.*, 1941, (Suppl.) cxv, 1-202.
72. WINKLER, A. W., LAVIETES, P. H., ROBBINS, C. L., and MAN, E. B.: Tolerance to oral thyroid and reaction to intravenous thyroxine in subjects without myxedema, *Jr. Clin. Invest.*, 1943, xxii, 535-544.
73. HARRIS, S. C., and IVY, A. C.: The influence of extrinsic gastro-intestinal innervation on dextrodine induced anorexia, *Federation Proc.*, 1946, v (pt. 2), 42.

74. HARRIS, S. C., IVY, A. C., and SEARLE, L. M.: The mechanism of amphetamine-induced loss of weight; a consideration of the theory of hunger and appetite, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 1468-1475.
75. BEYER, K. H.: The effect of benzedrine sulfate (beta-phenylisopropylamine) on metabolism and the cardiovascular system in man, *Jr. Pharmacol. and Exper. Therap.*, 1939, lxvi, 318-325.
76. American Medical Association: Council on Pharmacy and Chemistry. Personal communication to the authors.
77. Council on Pharmacy and Chemistry: Dinitrophenol not acceptable for N. N. R., *Jr. Am. Med. Assoc.*, 1935, cv, 31-33.
78. PELNER, LOUIS: The treatment of obesity by appetite control: the use of autonomic substances and their synergists, *Ann. Int. Med.*, 1945, xxii, 201-212.
79. KALB, S. W.: The fallacy of massage in the treatment of obesity, *Jr. New Jersey Med. Soc.*, 1944, lxi, 406-407.
80. SHORT, J. J., and CURRENCE, J. D.: An attempt to mobilize lipoids from storage depots by deep massage and increased tissue temperatures, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 395-397.



# THE POVERTY OF THE IMMUNOLOGICAL MECHANISM IN PATIENTS WITH HODGKIN'S DISEASE \*

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HODGKIN'S disease manifests itself as a proliferation of reticuloendothelial tissues, for which as yet no cause or causes have been established. Numerous kinds of bacteria have been found associated with this disease. Of these, many have in turn been proclaimed as the etiological agent only to be later unmasked as coincidental invaders. An interesting parallel to this fact is the increased susceptibility of these patients to intercurrent infections of various sorts; again here many different kinds of bacteria have been isolated. This greater susceptibility to infection seems paradoxical in the face of the massive proliferation of reticuloendothelial tissues, the cells of which, we have good reason to believe, are responsible for the production of antibodies.

In the light of this information it appeared desirable to examine the immunological mechanism of patients with Hodgkin's disease in the hope of elucidating some aspects of the pathogenesis (if not the etiology) of the disease. Accordingly a study was made of the case records of a large number of patients with Hodgkin's disease, with special reference to their immunological responses.

## MATERIAL

The material was obtained from several institutions in Memphis and Nashville in Tennessee, from Duke Hospital in Durham, North Carolina and from Charity Hospital in New Orleans. In Memphis the case records were studied at the John Gaston, the Baptist, the Methodist, and the Saint Joseph's Hospitals; while in Nashville the records were examined at the Vanderbilt and Nashville General Hospitals and at the Hubbard Hospital of the Meharry Medical College. In some of these institutions not all case records were available for study since the diagnosis file in the record room was of relatively recent introduction. Only those cases were studied in which the diagnosis was proved by biopsy or autopsy. Moreover, since the serological test for syphilis is a common procedure and, indeed, the immunological test most frequently used, the study was limited to those patients on whom such a test was done. Actually only a small number of patients were omitted because of this final restriction.

The names of patients of one institution were checked against those of the others in order not to include a patient more than once in the series. A few patients had visited more than one institution.

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TABLE I  
The Distribution of Age, Sex, and Color of Patients with Hodgkin's Disease According to Hospital Sources

White Males									White Females								
Age in Years	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	
John Gaston	0	3	5	2	1	2	0	0	1	0	0	1	0	1	1	0	
Baptist	0	0	0	1	1	1	0	0	0	1	0	0	0	0	0	0	
St. Joseph's	2	0	2	0	1	2	1	0	0	0	0	0	0	0	0	0	
Methodist	0	0	0	2	1	0	0	0	1	0	0	0	0	0	0	0	
Nashville General	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	
Vanderbilt	1	5	8	13	9	3	2	0	2	2	7	6	4	3	4	0	
Duke	0	7	15	15	9	7	2	1	1	4	3	4	2	2	2	0	
Charity	1	1	2	7	2	2	3	0	0	0	2	0	3	0	0	1	
Total White	4	16	32	40	25	18	8	1	2	8	12	11	9	6	8	1	

Colored Males									Colored Females								
Age in Years	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	
John Gaston	1	2	2	0	3	4	1	1	0	3	0	1	0	1	0	0	
Mcharry	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	
Vanderbilt	0	0	1	1	0	1	0	0	0	0	0	2	0	0	0	0	
Duke	5	0	3	2	1	0	1	0	0	0	3	2	0	0	0	0	
Charity	0	3	3	4	3	0	1	0	0	0	1	1	0	1	0	0	
Total Colored	6	5	9	8	8	6	3	1	0	3	4	6	0	2	0	0	
Total Both Races	10	21	41	48	33	24	11	2	2	11	16	17	9	8	8	1	

The following data were recorded in each case: name, age, sex, color and the results of all immunological studies made upon the patient. In all, the case records of 262 patients were examined.

### RESULTS

*Age, Sex, and Color Incidence.* The distribution of cases according to age, sex, and color is shown in table 1 and figure 1.

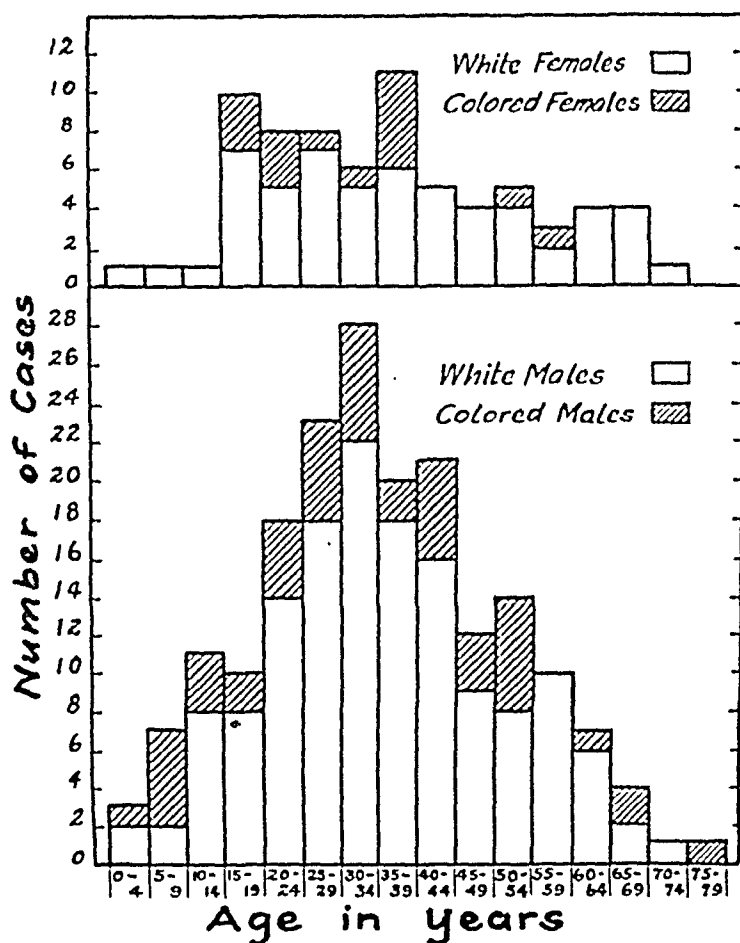


FIG. 1. Cases of Hodgkin's disease grouped according to sex, color and age (five year periods).

The age given is the one at which the diagnosis was first definitely established by an examination of the tissues; in the great majority of cases this was done by biopsy. In only a small number of cases (20) was the diagnosis first made at autopsy. Included in this series of patients were 144 white males, 57 white females, 46 colored males and 15 colored females. The ratio of males to females was 2.53 among the white patients, 3.07 among the colored patients, and 2.64 for both races.

An examination of figure 1 shows that very few cases occurred before the age of puberty. After puberty there was a sharp rise in the incidence

of the disease in both sexes, the bulk of the cases occurring in the reproductive period. Of a total of 72 female patients, three cases (4.2 per cent) were 14 years of age or less, 48 (66.7 per cent) between 15 and 44 years and 21 (29.2 per cent) over 44 years of age. Among the 190 male patients, 21 cases (11.1 per cent) were 14 years of age or less, 120 (63.2 per cent) between 15 and 44 years, and 49 (25.8 per cent) over 44 years of age.

*Syphilis.* Of the 61 colored patients, 10 (16.4 per cent) showed a positive serological test for syphilis. There were seven patients 10 years of age or less, of whom one had a positive Wassermann. The other 54 were 13 years of age or more, and of these nine (16.7 per cent) showed a positive reaction. This incidence is only about one-half that of the expected frequency (30 per cent) for colored adult patients.<sup>1, 2, 3, 4</sup>

Among the 201 white patients a positive serological reaction was present in seven (3.5 per cent). Fifteen patients were under 13 years of age and all of these showed negative tests; the seven positive cases occurred in the group of 186 adults. This incidence (3.8 per cent) approaches the expected frequency for white patients.

*Tuberculin.* The tuberculin skin test was done on 38 patients including 10 children and 28 adults. It was positive in only one patient who showed a 1 plus reaction to a dilution of 1/100. This is far lower than the expected frequency of about 50 per cent positive reactors.<sup>5, 6</sup>

There were three cases of associated active tuberculosis, but no tuberculin tests had been done on these patients.

*Typhoid.* Agglutination tests for the typhoid bacillus were done in 41 cases and for paratyphoid A and B in 32 cases—all with negative results.

TABLE II

Response of a Patient with Hodgkin's Disease to Inoculations of Typhoid Vaccine

Date	Sept. 20	Sept. 24	Sept. 30 (10 days)	Oct. 4 (14 days)	Oct. 12 (22 days)	Oct. 28 (38 days)
"H" Agglutinins	1:40		1:40	1:80	1:80	1:80
"O" Agglutinins	1:20		1:20	1:40	1:20	1:20
Inoculations of Vaccine	0.5 c.c.	0.75 c.c.	1 c.c.			

In addition a study was made of the ability of a patient with Hodgkin's disease to respond to typhoid vaccine.\* This patient (H. L.) was a 53 year old colored male who showed a 1 plus reaction to a 1/100 dilution of tuberculin and whose blood Kahn on admission was 1 plus; the latter reaction became negative three months later. He was given three intramuscular injections of typhoid-paratyphoid † vaccine over a period of 10 days; the volumes consisted respectively of .5 c.c., .75 c.c. and 1 c.c. Blood samples were taken before the course of vaccination and at 10, 14, 22 and 38 days respectively after the first inoculation. The results are shown in table 2. Before

\* The agglutination studies were done by Dr. I. D. Michelson of the Division of Pathology and Bacteriology, University of Tennessee College of Medicine.

† Parke-Davis Typhoid-Paratyphoid Vaccine containing 2000 million bacteria per c.c.

the course the level of the "H" agglutinins was 1:40 and that of the "O" agglutinins 1:20. After vaccination the "H" agglutinins reached a maximum of 1:80 and the "O" agglutinins 1:40. Obviously this patient was unable to respond to the typhoid antigen. At that time he was in good condition. Moreover, the value of his total blood proteins was 5.2 grams per cent which, though slightly reduced, is not low enough to explain his deficient antibody response on the basis of hypoproteinemia.<sup>7, 8, 9, 10</sup>

*Brucella.* The immunological tests for *Brucella* were uniformly negative in the group of patients from Memphis, Vanderbilt Hospital and Charity Hospital in contrast to the findings at Duke Hospital where some of the patients showed positive responses. But even in the latter group, in which there was a high incidence of brucellosis, the immunological reactions were deficient.

Among the group of patients from Memphis agglutination tests were done in 12 and were all negative. Negative results were also obtained from the skin test in two patients and the opsonin test in one. This group includes one patient from whose lymph node *Brucella* was cultured; his agglutination, skin and opsonin tests all showed negative results.

In the series from Vanderbilt the agglutination test was done in 27 patients and was negative in all. The skin and opsonin tests were also negative, the former in eight and the latter in two.

In the group from Charity Hospital the agglutination for *Brucella* is listed as positive in one of 13 cases.

At Duke Hospital the agglutination reactions were studied in 31 cases. Of these, four showed a positive agglutination above a dilution of 1:640; *Brucella* was cultured from these four patients. The skin test was done in nine cases and was positive in only one. The opsonin test was positive in six of 19 cases. The complement-fixation test which was done in 13 cases was negative in 10 and positive in three.

Wise and Poston<sup>11</sup> reported the immunological studies made upon seven of the Duke patients with Hodgkin's disease from whom *Brucella* was cultured. In spite of the coexistence of the *Brucella* infection the immunological responses were poor. The skin test was done on four of these patients and was negative in all. The complement-fixation test was positive in three and negative in three. In four patients the agglutinins and opsonins were present in significant concentration early in the course of the *Brucella* infection, but later disappeared in spite of the persistence of the bacteremia. In one patient *Brucella* was found intermittently over a period of 10 months, but all this time there were no demonstrable agglutinins; at the end of this period the patient finally developed a titer of 1:2,560. Another patient showed no immune responses in spite of the presence of *Brucella* during life. One patient gave negative agglutinin and opsonin tests; cultures during life were negative, but *Brucella* was found at autopsy. In a later paper on the coexistence of Hodgkin's disease and infection with *Brucella*, Forbus and

associates<sup>12</sup> summarized the experience at Duke University by saying that practically none of their patients showed specific antibody reactions in what they regarded as significant titer.

*Tularemia.* Agglutination tests were made in 41 cases; in 40 the result was negative and in one case it was positive in a 1:80 dilution. The skin test was done in one case and was negative.

*Proteus X-19.* The agglutination test was run on 20 patients, all with negative results.

*Miscellaneous.* Finally, the following miscellaneous immunological tests were negative: heterophile agglutinins in four cases, complement-fixation test for malaria in one, cold agglutinins in two, trichinella skin test in one, histoplasmin skin test in two, echinococcus skin test in two, agglutination test for Flexner bacillus in five, Frei test in one, and the complement-fixation test for amebiasis in one.

### DISCUSSION OF RESULTS

*Reaction to Tuberculin.* In the present series of patients, tuberculin tests were done on 38, with only one positive reaction. This incidence of 2.6 per cent is much below that of the expected frequency (about 50 per cent) for the general population.

Aronson<sup>5</sup> in 1931 made a study of the incidence of positive tuberculin reactions in the South. For Gibson and Lake Counties in Tennessee the incidence among white persons under 20 years of age ran about 54 per cent and 45 per cent respectively and for colored patients of the same age group 63 per cent and 56 per cent respectively. For persons over 20 years old the incidence was about 55 per cent for the white group and 80 per cent for the colored.

A current study by Dr. I. D. Michelson<sup>6</sup> of this Department of the incidence of tuberculin reactions among the patients of the John Gaston Hospital has shown a frequency of 52 per cent positive reactors among the general hospital population.

The tuberculin reaction in patients with Hodgkin's disease has been studied extensively. There is a good review of the subject in Wallhauser's article.<sup>13</sup>

Parker<sup>14</sup> states that "practically all authors are agreed that by far the great majority of cases of Hodgkin's disease give a negative reaction; even in cases with an associated active tuberculosis."

Steiner<sup>15</sup> found negative skin reactions to both avian and human tuberculin proteins in Hodgkin's disease.

Morquio<sup>16</sup> found the tuberculin test negative in patients with Hodgkin's disease even in those with associated tuberculosis. He believed that Hodgkin's disease causes a condition of anergy of the patient, by which the reaction to tuberculin is rendered negative, even when tuberculosis is present.

Bastai<sup>17</sup> reported 24 cases of Hodgkin's disease in which the tuberculin

reaction was studied. In 22 patients the reaction was negative and in only two was it slightly positive. This anergy he found to be absolute, even up to a dilution of 1:30. Moreover, this anergy occurred in both the early and late stages of the disease. Exceptionally, the tuberculin-allergy reappeared in patients who had roentgen-therapy and were in the stage of remission.

Marval<sup>18</sup> reported seeing patients with tuberculous lymphadenitis and intense tuberculin-allergy develop Hodgkin's disease (proved anatomically) with accompanying anergy to tuberculin. Moreover, he attempted active immunization with BCG in patients with Hodgkin's disease; as controls he had a group allergic to tuberculin and another normal non-allergic group. The last two groups became tuberculin positive, but the patients with Hodgkin's disease still remained tuberculin negative. He has found that patients with Hodgkin's disease can stand daily subcutaneous doses of as much as 2 c.c. of crude tuberculin without reaction. His patients with Hodgkin's disease were also anergic to avian tuberculin. He explains this tuberculin anergy by saying that since Hodgkin's disease is primarily a disease of the reticulo-endothelial system, patients with this disease would be inhibited in their reaction to tuberculin.

Evidently patients with Hodgkin's disease are anergic to tuberculin, even in the presence of active tuberculosis. This low incidence of reaction to tuberculin in patients with Hodgkin's disease cannot be explained by any protection against tuberculosis which Hodgkin's disease may confer, for if anything tuberculosis is more common among patients with this disease than among the general population.

*Syphilis.* There were 61 colored patients with Hodgkin's disease. Seven of these were 10 years of age or younger and one had congenital syphilis with a positive Wassermann reaction. The remaining 54 colored patients were 13 years of age or older; nine of these showed a positive serological test for syphilis. The incidence of a positive reaction among the colored adults was 16.7 per cent, which is about one-half the expected frequency of 30 per cent.

Of the 201 white patients there were 15 children all with negative serological reactions. The other 186 white patients were 13 years of age or more; of these seven showed a positive test. This gives an incidence of 3.8 per cent positive reactors for the white adult group. This approaches the incidence of syphilis among the white population in general.

The following data indicate the expected frequency of positive reactors among the white and colored populations. The recent survey of the population between the ages of 14 to 50 years in Jefferson County, Alabama<sup>1</sup> (which includes the city of Birmingham) showed that the incidence of syphilis among the colored group was 30.86 per cent and among the white 3.07 per cent. A study of syphilis among the draftees<sup>2</sup> (males between 21 to 35 years of age) gave the following incidence in Tennessee, North Carolina, and Louisiana:

Tennessee	Urban and Rural Combined	Urban—white	5.84 per cent
		colored	31.32 per cent
		Rural—white	2.96 per cent
		colored	22.89 per cent
North Carolina	Urban and Rural Combined	white	3.94 per cent
		colored	27.78 per cent
		Urban—white	3.42 per cent
		colored	32.36 per cent
	Urban and Rural Combined	Rural—white	2.61 per cent
		colored	19.40 per cent
		white	2.85 per cent
		colored	23.74 per cent
Louisiana	Urban and Rural Combined	Urban—white	4.53 per cent
		colored	31.79 per cent
		Rural—white	3.16 per cent
		colored	24.29 per cent
	Urban and Rural Combined	white	3.79 per cent
		colored	27.20 per cent

In 1940 the incidence of syphilis among the patients at Duke Hospital<sup>3</sup> was as follows: 29 per cent for the colored males, 32 per cent for the colored females, 2.7 per cent for the white males and 3.2 per cent for the white females.

At the Charity Hospital<sup>4</sup> a positive serological reaction was found in 26 per cent of the colored and in 6 per cent of the white patients.

The average incidence of syphilis among the colored patients at the John Gaston Hospital for the years 1940 to 1943 inclusive was 28 per cent. Since the group of cases of Hodgkin's disease occurred over many years the following additional control was set up for the colored group at the John Gaston Hospital: for each colored patient with Hodgkin's disease, a case record was picked at random to correspond to the same year, age, sex, and color. This was done twice; among the first control group about 40 per cent showed a positive Wassermann reaction and among the second about 32 per cent.

It is clear from these data that the expected frequency of a positive serological test among the colored adult population is about 30 per cent. Of our 54 adult colored cases of Hodgkin's disease 46 were accounted for by Duke Hospital, Charity Hospital, and the John Gaston Hospital. The incidence of positive reactions among the adult colored patients with Hodgkin's disease was 16.7 per cent, considerably lower than the expected frequency of 30 per cent. A statistical analysis, using the Chi-square method,<sup>10</sup> showed this difference to be significant.

Of the white adult patients with Hodgkin's disease 3.8 per cent had a positive serological test for syphilis. This approaches the expected fre-



quency among the white population in general. It should be pointed out, however, that since syphilis is 10 times more common among the colored than among the white population, more significance can be attached to our findings in the smaller group of colored patients with Hodgkin's disease than to our data derived from the white group.

Wallhauser<sup>13</sup> collected 268 cases of Hodgkin's disease from the literature in which the incidence of syphilis was studied. If to these are added the 60 cases of Krueger and Meyer,<sup>20</sup> nine positive reactors are found among 328 patients, or 2.7 per cent. These original articles do not state how many of the patients were colored. Certainly some colored patients were among the group, for in Simmons and Benet's article<sup>21</sup> there appear the photographs of two colored patients.

The significantly low incidence of positive serological reactions for syphilis in the group of colored patients with Hodgkin's disease requires explanation. It would seem unlikely that they are somehow protected against syphilis. It might be argued that this group was less exposed to syphilis owing to a generalized weakness and a loss of libido. This appears highly improbable, however, for it would require a considerable loss of strength to nullify so potent a stimulus among a group of colored adults. Probably, the explanation is similar to that for the anergy to tuberculin, namely, that patients with Hodgkin's disease are poor producers of antibodies. Syphilis probably occurs in a group of patients with Hodgkin's disease with the same frequency as among the general population, but owing to the poverty of their antibody production the incidence of a positive Wassermann reaction would be less among them than among the control group. For example, one of our colored patients (H. L.) on admission showed a 1 plus reaction to 1 mg. of tuberculin and a 1 plus Kahn reaction. Although he did not receive antisyphilitic treatment, one month later the Kahn reaction was negative. He died two months after the last examination and at autopsy a typical syphilitic aortitis was found.

*Typhoid.* Agglutination reactions for typhoid were done in 41 patients and for paratyphoid A and B in 32; all the results were negative. This, of course, is too limited an experience to be of any significance. I believe it significant, however, that one of the patients (H. L.) upon being given a course of typhoid vaccination was unable to produce antibodies. He was in good condition at the time, and the total protein of his blood was 5.2 grams per cent. This again points to an underlying inability to produce antibodies.

*Brucella.* At Duke University a rather high incidence of infection with *Brucella* was found coexistent with Hodgkin's disease. For example, in a series of 24 cases of Hodgkin's disease studied during life 14 yielded *Brucella* by cultures of either blood or lymph node. In spite of this, practically none of these patients developed specific antibody reactions against *Brucella* in what was regarded as significant titer.<sup>12</sup> This is further evidence of the deficiency of the antibody-production mechanism in Hodgkin's disease.

*Other Immunological Reactions.* As for the other immunological reactions observed in this series the data are insufficient to warrant any conclusions.

Davidsohn<sup>22</sup> reported that in patients with Hodgkin's disease some of the normal antibodies, namely the iso-agglutinins and the agglutinins for sheep red cells, were present in about the same titer as in normal persons.

### SIGNIFICANCE OF DATA

*Etiology and Pathogenesis.* It seems clear that patients with Hodgkin's disease are poor producers of antibodies. The anergy of these patients to tuberculin is well known, but the concept of anergy (failure of reactivity) should be enlarged to include a poor response to *all* types of antigens. The poverty of their antibody production mechanism is manifest not only in their inability to make the antibodies which are fixed to cells (such as in tuberculin hypersensitivity) but also the circulating antibodies of the types found in syphilis, brucellosis, and typhoid fever.

In view of the importance of the level of the blood proteins<sup>7, 8, 9, 10</sup> in the manufacture of antibodies it becomes necessary to study this factor in Hodgkin's disease. Starlinger and Winands<sup>23</sup> found that in Hodgkin's disease the blood shows a normal total protein, an absolute and relative increase in fibrinogen, a moderate absolute and relative increase in globulin and a significant absolute and relative decrease in albumin. In the terminal cachexia the protein content progressively decreases and the globulin returns to a normal value, with the relative increase preserved.

The plasma proteins were studied in eight patients at the John Gaston Hospital. The results, which are shown in table 3, are in accord with the findings of Starlinger and Winands.

TABLE III

Values in Grams Per Cent of Plasma Proteins in Eight Cases of Hodgkin's Disease at the John Gaston Hospital

Patient	Total Proteins	Albumin	Globulin	Fibrinogen
C. R. S.	5.3			
W. M.	4.6 (with edema)			
W. L.	7.5			
G. S.	5.5	3.2	1.1	1.2
H. L.	5.2	3.4	1.8	
E. C.	8.6	2.8	3.5	2.3
C. H.	6.2	2.8	2.6	0.8
H. J.	7.3	3.5	2.8	1.0

While the above data are limited, in that the various globulin fractions were not studied, it seems justifiable to say that the poor antibody response in Hodgkin's disease is not due to hypoproteinemia.

Since it has been suggested that antibody production might occur on the basis of proteolysis and proteosynthesis by the macrophage system,<sup>24</sup> the process of phagocytosis in Hodgkin's disease should be examined.

McJunkin<sup>25</sup> injected neutral red into a lymph node which showed typical Hodgkin's tissue. He found that the supravital reaction to neutral red of the large cells of Hodgkin's tissue was like that of the reticuloendothelium of normal and hypertrophied lymph nodes.

Mankin<sup>26</sup> in tissue culture studies of Hodgkin's tissue noted the development of two types of reticular cells. One was a variegated type of cell similar to that which developed in cultures of normal lymph nodes; this cell was phagocytic. The second type of cell, not found in cultures of normal nodes, was a "homogeneous" cell incapable of phagocytosis. As the cultures matured, the first type of cell lost its capacity of phagocytosis and appeared to go over to the second type; the latter increased in numbers and became the predominant reticular cell.

M. R. Lewis<sup>27</sup> noted that in tissue cultures of Hodgkin's tissue the Dorothy Reed cells were non-phagocytic.

This problem was studied recently in the case of H. L., the same patient who failed to respond to typhoid vaccine. This patient had an enlarged epitrochlear node, about 3 cm. in diameter. About 3 c.c. of a 1 per cent aqueous solution of trypan blue was injected intracutaneously and subcutaneously into the area drained by this node. Twenty-four hours later this node was removed. At the operation it was seen that all the tissues around the node were stained blue. Coursing over the capsule of the node were several small lymphatics which were stained a deep blue. The node itself, however, was unstained. Most of the tissue was fixed for microscopic study while the remainder was used for tissue culture. On microscopic examination no dye was found in the cells. This failure to take up the dye is not conclusive evidence of failure of phagocytosis since the afferent lymphatics might have been blocked by the proliferating Hodgkin's tissue.

Tissue cultures were made of some of the tissue removed at operation. At 24 and 48 hours there was a vigorous growth of macrophages and reticular cells. To these in vitro cultures trypan blue was added and after 24 hours' incubation the cultures were examined. There was no evidence of phagocytosis of the dye by the growing cells. Again it might be argued that this experiment is inconclusive in that the dye might not have penetrated the fine plasma coagulum in which the cells were growing. These studies will be pursued.

The data on phagocytosis in Hodgkin's disease are inadequate. More work must be done along these lines before any evaluation can be made of the rôle of this factor as a possible explanation for the anergy in this disease.

The next question that arises is whether this "total anergy" in Hodgkin's disease is a purely secondary phenomenon or whether it is a primary disturbance. The proponents of the former hypothesis may argue that in Hodgkin's disease the reticuloendothelial system becomes replaced by the Hodgkin's tissue so that its capacity to produce antibodies is interfered with. This explanation has been suggested by Morquio,<sup>16</sup> Marval<sup>28</sup> and Wall-

hauser.<sup>18</sup> The latter, in discussing the relationship between tuberculosis and Hodgkin's disease, states: "Probably a majority of students of the disease have considered *B. tuberculosis* as a secondary invader. If it is true, as many believe, that the lymphoid and reticulo-endothelial systems are concerned in the defense against tuberculosis it is hardly surprising that a lighting up of a tuberculous focus should occur when these systems have been practically eliminated or seriously injured by a disease such as lympho-granuloma."

Lillie<sup>28</sup> has suggested that the more frequent presence of organisms in Hodgkin's nodes may be accounted for by the lack of antibody-production by neoplastic reticuloendothelial tissue.

On the other hand, let us consider the hypothesis that in Hodgkin's disease the anergy is a primary phenomenon. The fundamental disturbance in Hodgkin's disease may be a primary metabolic dysfunction resulting in a deficiency of the enzyme system or systems necessary for proteolysis and proteosynthesis which occurs in antibody production. On the basis of this deficiency, one of many antigenic stimuli may set up a proliferation of reticuloendothelial tissues in an attempt to increase the cells which ordinarily make antibodies. This reticuloendothelial hyperplasia would normally result in increased antibody production; but in Hodgkin's disease there is merely a futile proliferation of functionless tissue. The cells are there, but their enzyme systems are deficient. According to this hypothesis, one would not expect to find a single etiological agent. In connection with this, one is reminded that the body has a limited number of ways of responding to injury, as illustrated by the multiplicity of stimuli which set off the response known as "inflammation."

A survey of the literature shows that only a few writers have been bold enough to suggest such an explanation. Brandt<sup>29</sup> believed that Hodgkin's disease is merely a manifestation of a severe damage to the reticuloendothelial system produced by various causes and not a disease of one kind alone. Desjardins,<sup>30</sup> impressed by the high frequency of diverse infections among patients with Hodgkin's disease, has suggested that chronic infections may start the disease.

Probably most students of the disease would prefer to accept the more orthodox explanation that the poor immunological mechanism in Hodgkin's disease is purely a secondary phenomenon resulting from the serious damage to the reticuloendothelial system. A characteristic response to the unorthodox suggestion that Hodgkin's disease may be caused by more than one etiological agent is that of Krumbhaar's<sup>31</sup> reaction to Desjardins' opinion. Krumbhaar wrote: "Desjardins' view that any chronic infection may start Hodgkin's as well as other lymphomatoid diseases in those hereditarily predisposed seems such a bad case of 'post hoc propter hoc' that it will probably obstruct progress but little." In spite of this criticism it seems to me that Desjardins' view merits consideration. At this point, both views should be considered

as equally probable; for certainly the evidence does not favor one over the other. An entrenched opinion that Hodgkin's disease must be caused by a single etiological agent may obstruct progress as much as any other opinionated viewpoint.

In any case, the poor immunological mechanism in Hodgkin's disease stands as a fact, regardless of whether it is a primary or a secondary event. Moreover, it serves to elucidate some of the factors associated with the disease. It probably explains the higher frequency of intercurrent infections and the increased susceptibility of these patients to infections. Also, it accounts for the finding of different kinds of bacteria in patients with this disease. It explains why, at various times, the tubercle bacillus,<sup>32, 33, 34, 35</sup> the diphtheroid bacillus,<sup>36, 37, 38</sup> *Brucella*<sup>11, 12, 39, 40</sup> and other bacteria have been isolated from the tissues of patients suffering from Hodgkin's disease. It should recommend caution to any investigator who, on finding a certain organism frequently associated with Hodgkin's disease, makes claims to it as the etiological agent.

*Treatment.* The finding of a deficient immunological mechanism in Hodgkin's disease would suggest that treatment, in addition to roentgen-therapy, should be directed along lines to stimulate antibody-production in order to increase resistance to infection. The diet should include a high proportion of proteins and other factors which have been shown to enhance antibody-production.

Recently pyridoxin<sup>41, 42, 43</sup> has been found to be essential for the manufacture of antibodies and the maintenance of lymphoid tissues. This substance was recently given to a patient (H. L.) shortly after the diagnosis was made. At that time the patient's general condition was rather good. In addition to roentgen-therapy, he was given 150 mg. of pyridoxin daily over a period of two months until his death. One was struck by the rapid worsening of his status, which went on to death in a matter of two months. Examination of the tissues at autopsy revealed a marked change in the histological picture of the Hodgkin's tissue. The picture had changed from the pleomorphic "granulomatous" appearance to that of a malignant neoplastic process, not unlike a reticulum cell sarcoma. Of course, it is not possible at this time to evaluate the rôle of pyridoxin in the acceleration of the hyperplasia which occurred in this case. In a few authenticated cases, Hodgkin's disease has progressed from a "granulomatous" to a "sarcomatous" phase. In view of the rôle of pyridoxin in the maintenance of lymphoid tissue, one wonders whether this substance was responsible for the increase in growth of the Hodgkin's tissue in this patient. The use of pyridoxin in the treatment of Hodgkin's disease should be studied further. Moreover, since pyridoxin maintains lymphoid tissue and may have accelerated the growth of the Hodgkin's tissue in this patient, a trial should be made of desoxypyridoxin,<sup>44</sup> a powerful inhibitor of pyridoxin. Indeed, Stoerk<sup>45</sup> has already speculated that desoxypyridoxin may be of use in the treatment of tumors of the lymphoid tissue.

## SUMMARY

Patients with Hodgkin's disease are deficient in their ability to produce antibodies. This deficiency is generalized and is illustrated by their anergy to tuberculin, by the lower incidence of positive serological tests for syphilis, by their inability to make antibodies against *Brucella* when brucellosis co-exists, and, in the case of one patient, by his inability to respond to typhoid vaccine.

This deficiency of the immunological mechanism cannot be explained on hypoproteinemia, since the total protein values are normal in these patients.

The rôle of the possible failure of phagocytosis has been discussed but there are insufficient data to draw any conclusions.

Consideration has been given as to whether this immunological deficiency is a secondary phenomenon subsequent to the damage of the reticuloendothelial system by a single etiological agent, or whether in Hodgkin's disease the primary disturbance is a metabolic one resulting in a deficiency of antibody production so that many different kinds of stimuli may cause a hyperplasia of Hodgkin's tissue as a compensatory, albeit futile, phenomenon.

In either case, this poverty of the immunological response of these patients explains their increased susceptibility to infection. Moreover, it explains why at various times different kinds of bacteria have been isolated from their tissues and proclaimed as the etiological agent.

It has been suggested that in the treatment of patients with Hodgkin's disease an attempt should be made to improve their ability to make antibodies in order to increase their resistance to infection. The use of high protein diet and pyridoxin in this regard has been discussed.

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## BIBLIOGRAPHY

1. SMITH, W. H. Y., and DENISON, G. A.: Blood testing and treatment program in Jefferson County, Alabama, Jr. Ven. Dis. Inform., 1946, xxvii, 94.
2. VONDERLEHR, R. A., and USILTON, L. J.: Syphilis among men of draft age in the United States, Jr. Am. Med. Assoc., 1942, cxx, 1369.
3. MOSELEY, V., CALLAWAY, J. L., and SHARPE, J. S.: A study of the incidence of syphilis in pregnant women and some results of therapy, Am. Jr. Obst. and Gynec., 1940, xxxix, 990.
4. MOSS, EMMA S.: Written communication.
5. ARONSON, J. D.: Incidence of tuberculous infection in some communities of the South, Am. Jr. Hyg., 1931, xiv, 374.
6. MICHELSON, I. D.: A study of the relationship between calcified pulmonary nodules, the presence of living tubercle bacilli, and tuberculin sensitivity (in preparation).
7. CANNON, P. R.: Antibodies and protein-reserves, Jr. Immunol., 1942, xlv, 107.

8. CANNON, P. R., CHASE, W. E., and WISSLER, R. W.: Relationship of protein-reserves to antibody production; effects of low-protein diet and of plasmapheresis upon formation of agglutinins, *Jr. Immunol.*, 1943, xlvii, 133.
9. WISSLER, R. W., WOOLRIDGE, R. L., and STEFFEE, C. H.: Influence of aminoacid feeding upon antibody production in protein depleted rats, *Proc. Soc. Exper. Biol. and Med.*, 1946, lxii, 199.
10. KREBS, E. G.: Depression of gamma globulin in hypoproteinemia due to malnutrition, *Jr. Lab. and Clin. Med.*, 1946, xxxi, 85.
11. WISE, N. B., and POSTON, M. A.: Coexistence of brucella infection and Hodgkin's disease; clinical, bacteriologic and immunologic study, *Jr. Am. Med. Assoc.*, 1940, cxv, 1976.
12. FORBUS, W. D., GODDARD, D. W., MARGOLIS, G., BROWN, I. W., JR., and KERBY, G. P.: Studies on Hodgkin's disease and its relation to infection by *Brucella*, *Am. Jr. Path.*, 1942, xviii, 745.
13. WALLHAUSER, A.: Hodgkin's disease, *Arch. Path.*, 1933, xvi, 522 and 672.
14. PARKER, F., JR., JACKSON, H., JR., FITZHUGH, G., and SPIES, T. D.: Studies of diseases of lymphoid and myeloid tissues; skin reactions to human and avian tuberculin, *Jr. Immunol.*, 1932, xxii, 277.
15. STEINER, P. E.: Skin reactions to avian and human tuberculinproteins in Hodgkin's disease, *Arch. Int. Med.*, 1934, liv, 11.
16. MORQUIO, L.: Sobre dos casos de linfogranulomatosis maligna conpleuresias serofibrinosas, *Arch. argent. de pediat.*, 1930, i, 573.
17. BASTAI, P.: Ueber die klinische Bedeutung der Tuberkulinanergie bei malignem Lymphogranulom, *Klin. Wchnschr.*, 1928, vii, 1606.
18. DE MARVAL, L.: Los pacientes afectados de linfogranulomatosis maligna son insensibles a dosis masivas de tuberculina bruta inyectada por via subcutanea, *Prensa méd. argent.*, 1940, xxvii, 2310.
19. MAINLAND, D.: The treatment of clinical and laboratory data, 1938, Oliver and Boyd, London.
20. KRUEGER, F. J., and MEYER, O. O.: Lymphogranulomatosis (Hodgkin's disease): review of 60 cases, *Jr. Lab. and Clin. Med.*, 1936, xxi, 682.
21. SIMMONS, C. C., and BENET, G.: Hodgkin's disease; a report on the cases observed at the Collis P. Huntington Memorial Hospital from April, 1913 to July, 1916 with special reference to treatment with radium and the X-ray, *Boston Med. and Surg. Jr.*, 1917, clxxvii, 819.
22. DAVIDSOHN, I.: Discussion of paper by Forbus and others,<sup>12</sup> *Am. Jr. Path.*, 1942, xviii, 745.
23. STARLINGER, W., and WINANDS, E.: Quoted by Wallhauser,<sup>13</sup> *Arch. Path.*, 1933, xvi, 522 and 672.
24. BURNETT, F. M.: The production of antibodies, 1941, MacMillan and Co., Ltd., Melbourne.
25. McJUNKIN, F. A.: Supravital reaction to neutral red of the cells of lymph nodes of Hodgkin's disease, *Arch. Path. and Lab. Med.*, 1926, ii, 815.
26. MANKIN, Z. W.: Experimentell-histologische Untersuchungen ueber normale und pathologisch veranderte Lymphknoten des Menschen, *Beitr. z. path. Anat. u. z. allg. Path.*, 1936, xcvi, 248.
27. LEWIS, M. R.: The behavior of Dorothy Reed cells in tissue cultures, *Am. Jr. Med. Sci.*, 1941, cci, 467.
28. LILLIE, R. D.: Discussion of paper by Forbus and others,<sup>12</sup> *Am. Jr. Path.*, 1942, xviii, 745.
29. BRANDT, M.: Beitrag zur pathologischen Anatomie der Lymphogranulomatose, *Virchow's Arch. f. path. Anat.*, 1929, cclxxii, 400.
30. DESJARDINS, A. U.: The etiology of lymphoblastoma, *Jr. Am. Med. Assoc.*, 1934, ciii, 1033.

31. KRUMBHAAR, E. B.: The present status of Hodgkin's disease, *in*: A symposium on the blood and blood-forming organs, 1939, The University of Wisconsin Press, Madison, pp. 148-166.
32. STERNBERG, C.: Quoted by Wallhauser,<sup>13</sup> Arch. Path., 1933, xvi, 522 and 672.
33. FRAENKEL, E., and MUCH, H.: Bemerkungen zur Aetiologie der Hodgkinschen Krankheit und der Leukaemia lymphatica, München. med. Wchnschr., 1910, lvii, 685.
34. L'ESPERANCE, E. S.: Experimental inoculation of chickens with Hodgkin's nodes, Jr. Immunol., 1929, xvi, 37.
35. L'ESPERANCE, E. S.: Study of a case of Hodgkin's disease in a child, Jr. Immunol., 1930, xviii, 127.
36. BUNTING, C. H., and YATES, J. L.: An etiologic study of Hodgkin's disease, Jr. Am. Med. Assoc., 1913, lxi, 1803.
37. BUNTING, C. H., and YATES, J. L.: An etiologic study of Hodgkin's disease, Jr. Am. Med. Assoc., 1914, lxii, 516.
38. BUNTING, C. H.: Hodgkin's disease, Bull. Johns Hopkins Hosp., 1914, xxv, 177.
39. PARSONS, P. B., and POSTON, M. A.: Pathology of human brucellosis; report of four cases with one autopsy, South. Med. Jr., 1939, xxxii, 7.
40. POSTON, M. A., and PARSONS, P. B.: Isolation of Brucella from lymph nodes of patients with Hodgkin's disease, Jr. Infect. Dis., 1940, lxvi, 86.
41. STOERK, H. C., and ZUCKER, T. F.: Nutritional effects on the development and atrophy of the thymus, Proc. Soc. Exper. Biol. and Med., 1944, lvi, 151.
42. STOERK, H. C., and EISEN, H. N.: Suppression of circulating antibodies in pyridoxin deficiency, Proc. Soc. Exper. Biol. and Med., 1946, lxii, 88.
43. STOERK, H. C.: Effects of calcium deficiency and pyridoxin deficiency on thymic atrophy (accidental involution), Proc. Soc. Exper. Biol. and Med., 1946, lxii, 90.
44. OTT, W. H.: Antipyridoxine activity of 2, 4-dimethyl-3 hydroxy-5-hydroxymethyl-pyridine in the chick, Proc. Soc. Exper. Biol. and Med., 1946, lxi, 125.



# CLINICALLY PRIMARY TUBERCULOUS PERICARDITIS \*

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TUBERCULOSIS of the pericardium is a more common finding for the pathologist than for the clinician. It more often occurs in the presence of demonstrable active tuberculous lesions elsewhere in the body, notably the lungs. Less frequently it occurs as a "primary" tuberculosis of the pericardium, or as a "clinically primary" tuberculosis of the pericardium. It is in the latter two that the etiological agent is frequently unsuspected: The tubercle bacillus is notoriously difficult to demonstrate in serous fluids or exudates, requiring exhaustive search over months in many instances. No one hesitates to make a diagnosis of tuberculosis of the pleura or peritoneum when other causes of pleurisy or peritonitis can be reasonably excluded.<sup>1</sup> Just as "clinically primary idiopathic pleurisy with effusion" is considered tuberculous in nature, unless proved otherwise, so should "clinically primary idiopathic pericarditis with effusion" be suspected as being tuberculous in nature. The "clinically primary" type of tuberculous pericarditis is that in which, at the onset of symptoms, there are no clinically demonstrable active tuberculous lesions elsewhere in the body,<sup>2</sup> although at some later date active foci may become demonstrable in other organs. This does not preclude the presence of hidden active foci at the onset. In distinction, primary tuberculosis of the pericardium, as defined by Thompson,<sup>3</sup> was that in which, as far as one could ascertain at autopsy, the pericardial involvement was either the only or the oldest tuberculous lesion. Rokitansky<sup>4</sup> is credited with being the first to comment on primary tuberculous pericarditis. He believed that it was dependent upon an earlier tuberculous lesion. Similarly, Harvey and Whitehill,<sup>1</sup> Blalock and Levy,<sup>5</sup> and Bellet, McMillan and Gouley<sup>6</sup> are of the same opinion. Hedbloom<sup>7</sup> apparently believes that primary tuberculous pericarditis does occur without the presence of any other previous tuberculous lesions. Recently, Terplan<sup>8</sup> has shown that a primary tuberculous focus can and does exist in the pulmonary parenchyma, with no involvement of the regional or mediastinal lymph nodes or lymphatic system. By inference drawn from this study, it may be possible for a primary tuberculous focus to exist in the pericardium.

The incidence of tuberculous pericarditis, in general, is not high. In an examination of 7,219 protocols, Norris<sup>9</sup> reported 1,780 tuberculous subjects, in which tuberculous pericarditis was present in 82, an incidence of 1.1 per cent. Likewise, Osler<sup>10</sup> in 1,000 autopsies reported 275 tuberculous subjects, of which seven had tuberculous pericarditis.

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In 1921, Hedbloom<sup>7</sup> collected 13 cases of primary tuberculous pericarditis. Rawls<sup>11</sup> added one case, and Thompson<sup>3</sup> in 1933, in a review of the literature, collected 21 cases of primary tuberculosis of the pericardium, to which he added seven more. Most of his cases were in the adhesive stage; apparently, only in one was the tubercle bacillus suspected ante mortem, the remaining being diagnosed correctly after autopsy examination.

Riesman,<sup>2</sup> in 1901, called attention to the "clinically primary" type of tuberculous pericarditis. Following this, other cases<sup>12, 13, 14, 15, 11, 16, 17</sup> of tuberculous pericarditis, falling within this category, appeared in the literature up to 1929, at which time Clark<sup>18</sup> in a careful search of the literature, found and reviewed 11 cases, and added two more of his own. Bellet, McMillan and Gouley,<sup>6</sup> in 1934, reported 17 cases of tuberculous pericarditis, of which they believed six to be clinically primary. Case histories were given in only two of the six. Platou,<sup>19</sup> Fine and Katz,<sup>20</sup> and Mackay<sup>21</sup> each reported a case of the clinically primary type. In Thompson's<sup>3</sup> series of seven cases we believe three to be of the clinically primary type, similarly six of Harvey and Whitehill's<sup>1</sup> cases belong in this classification. Babcock,<sup>22</sup> Burch and Winsor,<sup>23</sup> and Mitchell<sup>24</sup> each reported a case of tuberculous pericarditis, all of which appear to fall within this category. In Keefer's<sup>25</sup> 20 cases of tuberculosis of the pericardium, eight are apparently clinically primary. In a report of 42 cases, Blalock and Levy<sup>5</sup> stated that approximately seven were "primary from the clinical viewpoint." Cushing<sup>26</sup> and Cushing and Moritz<sup>27</sup> reported an interesting case which they believed to be a pericardial diverticulum and tuberculous pericardial effusion; however, at post mortem the lesion proved to be a tuberculous abscess of the anterior chest wall which communicated with the pericardial cavity. No other tuberculous lesions were found elsewhere in the body.

A total of 50 cases which we believe to be "clinically primary" tuberculous pericarditis have been collected from the literature, to which we add three of our own. This paper concerns itself with a discussion of several interesting findings in our cases and also an analysis of the symptoms and signs of the cases reviewed.

#### CASE REPORTS

*Case 1.* C. O., a white male, aged 60, was admitted June 6, 1941, with the complaint of headache and fever of two weeks' duration. Two weeks prior to admittance he was in an automobile accident, at which time he was temporarily unconscious and fever up to 103° F. appeared. Several days prior to entry a slight productive cough developed. There was no history of tuberculosis.

Physical examination revealed a well developed and nourished male who appeared acutely ill, with a fever of 103.4° F., pulse rate of 90, respiratory rate of 24, and blood pressure 100 mm. Hg systolic and 65 mm. diastolic. Lungs were clear. Cardiac dullness appeared within normal limits, with normal rhythm and no murmurs. Abdomen was negative.

Urinalysis showed trace of albumin, an occasional hyaline cast, and red and white cells. Hemoglobin was 13.5 grams. Leukocyte count was 8,050 with normal dis-

tribution. Tuberculin skin test was positive to 1:100 dilution of old tuberculin. Roentgenograms of chest revealed a cardiac silhouette of water-bottle type, indicating pericardial effusion; and minimal left pleural effusion. The only pulmonary pathologic lesion was a calcified Ghon primary lesion in the left base. Electrocardiogram revealed changes consistent with pericardial involvement.

Course: A pericardiocentesis performed 10 days after entry yielded 150 c.c. of cloudy yellow fluid, which was positive for tubercle bacilli on guinea pig necropsy six weeks later. About two weeks after entry a palpable but non-tender liver was noted. Auricular fibrillation appeared also at this time for which the patient was digitalized. Improvement followed for the next five months, during which time the size of the cardiac shadow decreased slightly. A year after entry a roentgenogram revealed the presence of a right pleural effusion and the cardiac shadow still enlarged. Right thoracentesis was performed and 850 c.c. of amber colored fluid were removed, which was negative for tubercle bacilli on guinea pig inoculation. In July 1942 the patient became suddenly very dyspneic. The liver was tender and extended several fingers'-breadth below the right costal margin, but no ascites nor peripheral edema was demonstrable. A pericardiocentesis was performed and 600 c.c. of fluid were removed, with relief to the patient. At this time pneumopericardium was instituted. Several days later dyspnea recurred, associated with a fever of 102° F. A right thoracentesis was performed, with removal of 2,000 c.c. of fluid, which was negative for tubercle bacilli on guinea pig inoculation. Between July and November of 1942 the patient received six pericardiocenteses, the largest amount of fluid withdrawn being 1,200 c.c. Pneumopericardium was maintained following each tap. Over the subsequent 11 months two courses of tuberculin therapy were given with seemingly beneficial results.\* Several attempts at removal of pericardial fluid were made during June 1943, but no fluid was obtained. Fluoroscopy and roentgenograms showed the cardiac shadow decreasing in size. Improvement continued except for occasional episodes of dyspnea and right upper quadrant pain. The patient was discharged in September 1943, asymptomatic and ambulatory, the heart appearing normal in size. No pulmonary lesion had been demonstrable, as yet.

Patient was readmitted January 20, 1944, complaining of fainting; however, he left the hospital the next day, prior to workup and against medical advice.

Patient was admitted for the third time on March 16, 1944, with a fever of 102° F., pulse rate 120, respirations 24, complaining of fatigue, shortness of breath and a mild productive cough. Examination revealed râles and wheezes in both lung bases. The area of cardiac dullness was normal, heart tones were distant, and gallop rhythm was present. Sputum was negative for acid-fast bacilli on smear. He improved on symptomatic treatment and was discharged on April 11, 1945.

Patient was admitted for the fourth time on January 31, 1946, because of orthopnea and indigestion. Temperature was 98.6° F., pulse 88 and respirations 22. The lungs were clear. The heart was not enlarged, the tones distant, rhythm regular and no murmurs were audible. The abdomen revealed ascites and a paracentesis was performed, with removal of 1,000 c.c. of dark green fluid. Ascitic fluid, gastric contents and urine were all negative on smear and guinea pig inoculation. The patient improved and was discharged on March 29, 1946.

The patient's final entry was on April 24, 1946, complaining of dyspnea. Examination revealed ascites, for which a paracentesis was done and 400 c.c. of clear amber colored fluid were removed, which proved negative for tubercle bacilli on smear. The cephalin cholesterol flocculation test was 3 plus. Serum proteins were 6.54 gm./100 c.c. Blood urea nitrogen was 23 mg./100 c.c. and the non-protein nitrogen 37 mg./100 c.c. The patient's course was progressively downward and he died on June 13, 1946.

\* Results to be discussed in another paper at a later date.

Necropsy findings: Adhesive and fibrotic pericardio-mediastinitis; portal cirrhosis and ascites; young miliary tubercles of the myocardium, liver and lungs.

*Case 2.* L. A., a white male, 42 years of age, was admitted on November 13, 1944, complaining of shortness of breath, weakness and cough of one and one-half months' duration. The patient was well until one and one-half months ago when he developed a slightly productive cough, associated with weakness and shortness of breath. He was examined physically and fluoroscopically several times by his doctor, and the only positive finding was "enlarged heart." There had been a loss of 20 pounds in weight over this period of time. The past history was non-contributory, except for the fact that both his parents had been ill with "pneumonia" for the past several months. Physical examination revealed a thin man, appearing chronically ill, with a temperature of 100.4° F., pulse 85, respirations 22, blood pressure 110 mm. Hg systolic and 70 mm. diastolic. The chest was thin. The resonance, breath sounds, and vocal fremitus at the right lung base were decreased. The outline of the heart was not determinable upon percussion, nor was the point of maximum intensity palpable. A high pitched systolic murmur was heard to the left of the sternum in the fourth interspace. The abdomen was protuberant, and no organs were palpable.

Hemoglobin was 12.5 gm., leukocyte count was 6000 with 84 per cent neutrophils and 16 per cent lymphocytes. There were occasional red and white blood cells in the urine. Several 24-hour sputum specimens were negative for acid-fast bacilli on smear. Tuberculin skin test was negative to 1.0 mg. old tuberculin. The electrocardiogram showed sinus tachycardia and low QRS in all leads. Roentgenograms of the chest revealed no evidence of active pulmonary disease, but the heart was markedly enlarged to both sides.

*Course:* The patient ran an intermittent type of fever, between 99° and 102° F. About 10 days after entry he became quite dyspneic, the neck veins were distended, and a friction rub near the apex became audible. Pericardiocentesis was performed, with removal of 150 c.c. of straw-colored fluid, which proved to be positive for the tubercle bacillus on smear. The patient's distress was slightly relieved following this. Bilateral pleural effusion appeared one month after entry, requiring removal of fluid for relief. A total of three left and 12 right thoracenteses and seven pericardiocenteses were done. Pneumopericardium and pneumothoraces were maintained until death on March 28, 1945.

*Necropsy findings:* A markedly thickened pericardium, multiple bilateral pericardio-diaphragmatic adhesions; miliary tubercles in lungs, pleurae, liver, spleen, kidneys, and peritoneum.

*Case 3.* P. C., a Negro male, 30 years of age, was admitted on March 30, 1945, complaining of shortness of breath of four days' duration. About three weeks before entry the patient developed a dry cough, with chills and fever. Four days previously he began to experience difficulty in breathing associated with a choking sensation. The physical examination revealed a well developed and nourished Negro in obvious respiratory distress. The temperature was 103.6° F., pulse 84, respirations 24 and blood pressure 120 mm. Hg systolic and 90 mm. diastolic. The tonsils were enlarged and the mucous membranes injected. No lymphadenopathy was present. Lungs were clear. The area of cardiac dullness was enlarged to the left and right, and heart tones were faint, rhythm regular and no murmurs were heard, but a friction rub was present to the left of the sternum in the fourth interspace. The liver was tender and palpable several fingers'-breadth below the right costal margin. The remaining examination was negative.

Hemoglobin was 11.7 gm. and red blood cell count was 4.1 millions. A leukocyte count was 7,000 with 90 per cent neutrophils and 10 per cent lymphocytes. All sputum examinations were negative, and the tuberculin skin test was positive to

1:10,000 old tuberculin. The electrocardiogram showed low amplitude in Leads I and II, with inverted T-waves in all leads and sinus tachycardia. Fluoroscopy and roentgenograms revealed a waterbottle shaped heart and clear lung fields.

Course: Two days after entry a pericardial tap was done, with removal of 400 c.c. of bloody fluid. The patient felt greatly relieved. The pericardial fluid was negative for acid-fast bacilli on both smear and guinea pig inoculation. Barium meal showed antero-posterior compression of the esophagus, due to the effusion, with delayed filling of the stomach. Smear of stomach contents obtained by gastric lavage performed a month after entry revealed occasional acid-fast bacilli. The patient was fairly comfortable until about three months later, when he became dyspneic again, and was found to have left pleural effusion. Thoracentesis was performed, and the fluid was proved positive for tuberculosis by means of guinea pig inoculation. Subsequently, right pleural effusion and ascites developed, and also evidence of cardiac failure, requiring digitalization. His fever ranged from 99° to 103° F., and he was dyspneic continually during the remainder of his course. Seven months after entry he began to expectorate foul smelling sputum in large quantities. Fluoroscopy showed an infiltration in the left lung, with a small apical cavity. He died on October 6, 1945.

Necropsy findings: Adherent and thickened pericardium; multiple cavitations in the left lung; tuberculous enteritis and ascites.

## DISCUSSION

One of the cases cited (case 1) shows that these patients may tolerate a relatively large pericardial effusion over a considerable time. This can be explained on the basis that the accumulation of fluid in the pericardial cavity is sufficiently slow to allow the pericardium to accommodate itself to the increased distention, thereby allowing the intra-pericardial pressure to remain below the level which causes serious embarrassment to the circulation.<sup>7</sup> This patient tolerated a pericardial effusion for approximately 24 months. The last pericardiocentesis to yield fluid was performed 16 months after the initial one. Several unsuccessful attempts to remove fluid from the pericardial cavity were performed 24 months after the onset of the effusion.

Pneumopericardium is helpful in both diagnosis and treatment. Upon production of a pneumopericardium, the findings of a normal sized heart, a thickened pericardium, and the absence of murmurs point strongly to tuberculosis as the causative factor. In treatment it offers the possibility of limiting the tuberculous exudate to the pericardial cavity, thereby averting a later adhesive pericarditis.<sup>7, 28</sup> Others<sup>23</sup> doubt its value and believe that it may increase fibrosis. Ackermann<sup>29</sup> believes it to be beneficial.

In case 2, the interesting findings were a tuberculin skin test negative to 1.0 mg. of old tuberculin, and the rapid accumulation of fluid, necessitating frequent removal from both pericardial and pleural cavities for relief. Apparently, the process was so acute and fulminating that sensitivity to tuberculin had not developed, thus substantiating the fact that a positive tuberculin skin test is not absolutely essential to denote the presence of a tuberculous condition in the body.

In case 3, although acid-fast bacilli were not found in the pericardial fluid,

the clinical picture was sufficiently adequate for the diagnosis of tuberculous pericarditis to be made. Finding tubercle bacilli later in the gastric contents proved the nature of the etiological agent, during which time the pericardial involvement was still the prominent feature of the case.

*Analysis of Cases:* We have attempted to analyze the prominent clinical findings of clinically primary tuberculous pericarditis; however, sufficient data are available in only 37 of the cases in this study. These findings are shown in table 1.

**Age:** The ages ranged from 9 to 80 years, of which 15 (41 per cent) were within the first three decades and the remaining 22 cases (59 per cent) after the third decade of life.

**Sex:** Twenty-nine (79 per cent) cases were males.

**Race:** In only 29 of the 37 cases was the race stated. Sixteen (43 per cent) were colored, the remaining 13 (35 per cent) being white. This dis-

TABLE I

Prevailing Findings in 37 Cases of Clinically Primary Tuberculous Pericarditis

(1) <i>Age</i>		(6) <i>Laboratory Findings</i>	
0-15 years old	5 (14%)	(a) Leukocyte count	
16-30	10 (27%)	Normal	15 (41%)
31-45	7 (18%)	Leukocytosis	6 (16%)
46-60	11 (30%)	Leukopenia	4 (11%)
61 and over	4 (11%)	Not reported	12 (37%)
(2) <i>Sex</i>		(b) Tuberculin skin test	
Male	29 (79%)	Positive	16 (43%)
Female	8 (21%)	Negative	1 (3%)
(3) <i>Race</i>		Not reported	20 (54%)
Colored	16 (43%)	(c) Diagnosis based on:	
White	13 (35%)	Guinea pig inoculation	13 (35%)
Unknown	8 (22%)	Smear	6 (16%)
(4) <i>Presenting Symptoms</i>		Culture	1 (3%)
(a) Fever	33 (89%)	Autopsy	17 (46%)
99-100° F.	5 (15%)	(7) <i>Duration of Illness</i>	
101-103° F.	16 (48%)	0-6 months	23 (63%)
above 103° F.	12 (37%)	7-12 months	8 (21%)
(b) Shortness of breath	28 (76%)	13-24 months	3 (8%)
(c) Edema	25 (68%)	over 2 years	3 (8%)
(d) Cough	19 (51%)	(8) <i>Outcome</i>	
(e) Weakness	16 (43%)	Died	31 (84%)
(f) Chest pain	13 (35%)	Improved or "recovered"	6 (16%)
(g) Headache	4 (11%)		
(h) Abdominal pain	4 (11%)		
(5) <i>Prominent Physical Findings</i>			
(a) Distended neck veins	12 (37%)		
(b) Pericardial friction rub	8 (21%)		
(c) Arrhythmias	10 (27%)		
(d) Pericardial effusion	24 (65%)		
(e) Pleural effusion	21 (57%)		
Bilateral	12 (57%)		
Left only	6 (29%)		
Right only	3 (14%)		
(f) Ascites	15 (41%)		
(g) Palpable liver	9 (24%)		

tribution is of interest because the incidence of tuberculous pericarditis in general, as described in the literature, is much higher than the above figures for the negro race.

**Symptoms and Signs:** Fever and shortness of breath occurred with the greatest frequency, the former being present in 33 (89 per cent) of the cases, the latter in 28 (76 per cent). Of the 33 with fever, 5 (15 per cent) were below 100° F.; 16 (48 per cent) from 101 to 103°, and 12 (37 per cent) over 103° F. A high fluctuating temperature prevailed, but no typical curve was found. Dependent edema was common, occurring in 25 (68 per cent) of the cases. Cough and weakness were present in about half the cases. Chest pain occurred in one third of the cases, its location being variable, and was not severe. Headache and abdominal pain were not common, each happening in only four (11 per cent) cases. Distention of the neck veins, indicating increased intra-pericardial pressure, was present in 12 (37 per cent) cases. (Experimental work indicates that approximately 100 c.c. of pericardial fluid will initiate a rise in venous pressure.<sup>30</sup>) Pericardial effusion was present in 24 (65 per cent) cases and pericardial friction rub in only eight (21 per cent). Friction rubs occurred in those cases with effusion as well as those without. In most cases the pericardial fluid was sero-sanguineous in nature. The amount of fluid removed at a single tapping varied from 50 to 2,500 c.c. The effusions recurred frequently, necessitating repeated pericardiocenteses for relief of symptoms in many of the cases. In almost all cases in which they were performed, both roentgenography following pneumopericardium and postmortem examination revealed the presence of a normal sized heart and the absence of valvular disease. Distant heart tones and an absent apical impulse were common findings. Cardiac arrhythmias occurred in 10 (27 per cent) cases, auricular fibrillation being present in five, paradoxical pulse in four, and partial heart block in one. Sinus tachycardia was common in most cases. The electrocardiogram consistently revealed low voltage and changes in the S-T segment and T-waves. Pleural effusion occurred in 21 (57 per cent), 12 being bilateral; effusion was twice as common on the left as on the right, when unilateral. The presence of ascites was shown in 15 (41 per cent) and an enlarged palpable liver in only nine (24 per cent) cases. The leukocyte count was reported in 25, a mild leukocytosis being present in six (24 per cent), a leukopenia in four (16 per cent), and in the remaining 15 (60 per cent) cases was within normal limits. This uncommon occurrence of leukocytosis has been noted by others.<sup>1, 23</sup> It is worthwhile to note the disproportion between the fever and leukocyte count, which may prove to be an important differential point. In only 17 of the 37 cases was the tuberculin test mentioned. All were positive with the exception of one (case 2 in our series). This case was negative to 1.0 mg. of old tuberculin. An uncommon finding was jaundice, present in two cases.<sup>10, 21</sup> A choking sensation occurred in one. Other symptoms that are common to tuberculosis in the body were night sweats and weight loss. Finding of the tubercle bacillus was difficult in most cases,

requiring repeated smears, cultures, and guinea pig inoculations from all available sources. Many cases required months to demonstrate the organism. In 17 (46 per cent) cases the diagnosis was definitely established only at post mortem.

The duration of the illness lasted six months or less in the majority of cases (23 or 63 per cent). Only six (16 per cent) lived over one year. The duration of case 1 in our series is apparently the longest reported in the literature, lasting for five years before terminating fatally owing to miliary tuberculosis.

Nearly all cases (31 or 84 per cent) had a fatal outcome. Only six (16 per cent) were reported improved; surgical intervention was employed in several cases.<sup>7, 22</sup> However, the final results in these improved cases are unknown. It is conjectured that these improved cases might have simulated case 1, in that the latter was discharged improved five times, only to terminate fatally as a result of his primary disease.

Many<sup>1, 18</sup> believe that the commonest cause of death in the younger patients with tuberculous pericarditis is miliary tuberculosis, and that in the older age group is myocardial failure.

### SUMMARY AND CONCLUSIONS

Fifty cases of clinically primary tuberculous pericarditis have been collected from a review of the literature, to which three cases of our own have been added. The findings in 37 cases with adequate data are analyzed.

Involvement of the pericardium as the first clinical manifestation of active tuberculosis is not rare. The diagnosis should be seriously considered when: (a) there are presenting symptoms of unexplained fever, shortness of breath, edema, cough, weakness and chest pain; (b) there is evidence of pericardial involvement, viz. friction rub, effusion and characteristic abnormalities in the roentgenogram; (c) these findings are present in a male over 30 years of age, and of the colored race.

Emphasis is placed on the necessity of frequent and persistent examination of all materials available in order to find the tubercle bacillus. Failure to demonstrate them does not necessarily rule out the clinical diagnosis, as shown by the fact that almost half of the cases analyzed required postmortem confirmation.

Prognosis is unfavorable, most cases terminating fatally within a year.

### BIBLIOGRAPHY

1. HARVEY, A. M., and WHITEHILL, M. R.: Tuberculous pericarditis, *Medicine*, 1937, xvi, 45.
2. RIESMAN, D.: Primary tuberculosis of the pericardium, *Am. Jr. Med. Sci.*, 1901, cxxii, 6.
3. THOMPSON, W. P.: Primary tuberculosis of the pericardium, *Jr. Am. Med. Assoc.*, 1933, c, 642.
4. ROKITANSKY, C.: A manual of pathological anatomy, London, The Sydenham Society (cited by Harvey and Whitehill).
5. BLALOCK, A., and LEVY, S. E.: Tuberculous pericarditis, *Jr. Thoracic Surg.*, 1937, vii, 132.



6. BELLET, S., McMILLAN, T. M., and GOULEY, B. A.: Tuberculous pericarditis; clinical and pathological study based on series of 17 cases, *Med. Clin. N. Am.*, 1934, xviii, 201.
7. HEDBLOOM, C. A.: Primary tuberculous pericarditis, *Surg. Clin. N. Am.*, 1921, i, 1411.
8. TERPLAN, KORNEL: Anatomical studies on human tuberculosis; primary tuberculous focus without lymph node changes in adults, *Supplement to the Am. Rev. Tuberc.*, 1940, xlii, 168. Anatomical studies of human tuberculosis; primary foci without lymph node changes. Additional observations, *Am. Rev. Tuberc.*, 1946, liii, 393.
9. NORRIS, G. W.: Cardiac pathology, 1911, W. B. Saunders Co., Philadelphia, Pa.
10. OSLER, W.: *Am. Jr. Med. Sci.*, 1893, cv, 20 (cited by Dillon).
11. RAWLS, W. B.: Primary tuberculous pericarditis, *Am. Jr. Med. Sci.*, 1925, clxix, 815.
12. NORRIS, G. W.: Tuberculous pericarditis, *Univ. Penn. Med. Bull.*, 1904, xvii, 155.
13. THAYER, W. S.: Observations of 2 cases of tuberculous pericarditis with effusion, *Johns Hopkins Med. Bull.*, 1904, xv, 149.
14. EHRENCLOU, A. H.: Acute tuberculous pericarditis, *U. S. Navy Med. Bull.*, 1921, xv, 120.
15. JAUCH, F. J.: Tuberculous pericarditis, *Brit. Med. Jr.*, 1922, i, 798.
16. DILLON, E. S.: Tuberculous pericarditis with tuberculosis of the myocardium and endocardium, *Med. Clin. N. Am.*, 1926, x, 253.
17. BLATT, M. L., and GREENGARD, J.: Pericarditis as primary clinical manifestation of tuberculosis in childhood, *Am. Jr. Dis. Child.*, 1928, xxxv, 631.
18. CLARK, J. A., JR.: Clinically primary tuberculous pericarditis, *Am. Jr. Med. Sci.*, 1929, clxxvii, 115.
19. PLATOU, R. V.: Clinically manifest tuberculous pericarditis, *Am. Jr. Dis. Child.*, 1939, lvii, 1386.
20. KATZ, S., and FINE, M. J.: Clinically primary tuberculosis of the pericardium, *Dis. Chest*, 1944, x, 60.
21. MACKAY, N. R.: Tuberculous pericarditis and clinically primary tuberculous pericarditis, *New Zealand Med. Jr.*, 1937, xxxvi, 41.
22. BARCOCK, W. W.: Tuberculous pericarditis with enormous effusion; pericardotomy, *Surg. Clin. N. Am.*, 1934, xiv, 39.
23. BURCH, G. E., and WINSOR, T.: Tuberculous pericarditis with effusion, *Clinics*, 1942, i, 166.
24. MITCHELL, G. F.: Tuberculous pericarditis and Pick's disease, *Arch. Pediat.*, 1938, lv, 157.
25. KEEFER, C.: Tuberculosis of the pericardium; study of 20 cases, *Ann. Int. Med.*, 1937, x, 1085.
26. CUSHING, E. H.: Diverticulum of pericardium, *Arch. Int. Med.*, 1937, lix, 56.
27. CUSHING, E. H., and MORITZ, A.: Diverticulum of pericardium; further data showing presence of extra-thoracic abscess, *Arch. Int. Med.*, 1937, lx, 482.
28. WHITE, P. D.: Heart disease, 1938, The Macmillan Co., New York.
29. ACKERMANN, W.: Treatment of pericarditis with effusion by injections of air and lipiodol into pericardial sac, *Am. Rev. Tuberc.*, 1931, xxiv, 98.
30. FINEBERG, M. H.: Functional capacity of normal pericardium; experimental study, *Am. Heart Jr.*, 1936, xi, 748.

# THE EFFICACY OF MAINTENANCE DOSES OF DIGITALIS IN PREVENTING THE RECURRENCE OF CONGESTIVE HEART FAILURE \*

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## INTRODUCTION

SEVERAL investigators<sup>1</sup> have demonstrated that patients with heart disease associated with auricular fibrillation develop congestive heart failure when digitalis is withheld. Katz, Sokolow, Weinberg and Plaut<sup>2</sup> were the first investigators to study the effect of maintenance doses of *folia digitalis* on the circulation of patients with chronic congestive heart failure associated with regular sinus rhythm. They presented studies on four patients who showed a prompt increase in the venous pressure, circulation time, and weight when digitalis was withheld and who also developed clinical evidence of congestive heart failure. We had begun a similar study several months before the publication of this work.

## METHOD AND MATERIALS

One hundred and four patients with heart disease associated with regular sinus rhythm who had been discharged from Charity Hospital after treatment for congestive heart failure were followed in the clinic at intervals of from one to four weeks over a period of from six months to two years. At the time the study was begun most of the patients had been taking 0.1 to 0.3 gm. of *folia digitalis* for several weeks or months after discharge from the hospital. Measurements of venous pressure, circulation time, vital capacity and weight were made during a one to three month period at intervals of from one to four weeks; then digitalis was discontinued and the same measurements repeated at the same intervals of time. The degree of dyspnea, orthopnea and edema was recorded as well as the presence or absence of râles, the size of the liver, the cardiac findings and the subjective state of the patient. Patients were advised to avoid sudden exertion of any kind, limit the fluid and salt intake insofar as possible and report to the clinic whenever they developed a cough, other evidence of infection or increasing symptoms of congestive heart failure.

## RESULTS

Of the 104 patients 79 were colored and 25 were white. There were 60 males and 44 females with an age incidence of from 31 to 80. Sixty-one had

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hypertensive cardiovascular disease, 21 arteriosclerotic, 2 rheumatic and 20 syphilitic.

The data were broken down according to the variation in the measurements of the venous pressure, circulation time, vital capacity, weight, heart size and frequency of the development of congestive heart failure while the patients were being studied.

In general it can be stated that none of the criteria employed for measurement of the circulation revealed any significant differences during the time digitalis was given to the patient and during the period that the drug was withheld. In no instance did we find a patient showing a consistent increase in venous pressure, circulation time and weight when digitalis was withheld with a prompt reversal of these measurements when the drug was readministered.

TABLE I.

The variations and averages of the measurements of the vital capacity, venous pressure, circulation time and weight are shown for nine patients with heart disease during the periods when they were taking maintenance doses of folia digitalis and during the time when the drug was being withheld. See text.

Pt.	Vital Capacity in Liters		Circulation Time in Seconds		Venous Pressure in Cm. of Water		Weight in Pounds	
	Without Digitalis	With Digitalis	Without Digitalis	With Digitalis	Without Digitalis	With Digitalis	Without Digitalis	With Digitalis
3	2.50-2.12 (2.31)	2.83-1.70 (2.12)	35-30 (32)	36-24 (27)	22-12 (13.5)	16-7.5 (8.6)	154-142 (146)	150-138 (142)
21	1.42-2.12 (1.65)	2.27-2.03 (2.12)	28-25 (28)	40-35 (35)	30-12 (18)	28-9.8 (17.9)	133-118 (122)	129-121 (124)
26	3.82-3.31 (3.40)	3.97-3.35 (3.54)	37-27 (31.4)	43-20 (31.4)	17-8 (12.9)	14-9 (10.4)	141-135 (139)	139-131 (133)
35	2.60-2.12 (2.36)	2.60-2.12 (2.41)	30-19 (24.2)	28-10 (20.8)	16-11 (13.7)	19-8 (13.2)	176-165 (170)	175-163 (170)
36	2.17-1.65 (1.98)	2.12-1.94 (2.03)	17-13 (15)	15-12 (13.7)	15-8 (12.5)	11.5-6.5 (8.2)	133-123 (130)	127-120 (123)
45	1.94-1.42 (1.65)	2.36-1.42 (1.84)	18.5-11 (14)	20-9.5 (13.6)	20-17 (13.3)	27-10 (10.7)	231-228 (229)	236-225 (229)
50	2.74-1.56 (2.50)	3.40-2.55 (2.93)	35-14 (23.6)	25-20 (23.2)	21-6 (11.2)	11-7.5 (9.4)	159-146 (152)	158-144 (151)
57	2.64-146 (2.27)	2.41-2.12 (2.30)	43-35 (38)	36-21 (30)	21-7.5 (16.5)	11-8 (10.5)	212-200 (206)	204-194 (199)
63	2.31-1.23 (1.75)	2.27-2.12 (2.23)	16-12 (15.5)	16-13 (14.7)	17-12 (14)	18-8.5 (14)	187-160 (173)	180-177 (178)

Table 1 presents the variation and averages in the measurements of vital capacity, circulation time, venous pressure and weight for the 10 patients showing the most clear-cut differences in these measurements in the two periods of study. At least four and as high as 20 separate measurements

of the vital capacity, circulation time, venous pressure and weight were made during each period: First, when the patient was receiving maintenance doses of *folia digitalis* of from 0.1 to 0.3 gm. and, second, when the drug was withheld. It can be seen that there was a marked overlapping of the measurements in every instance and that the average differences between any of the measurements in the two periods are not statistically significant. Data for the remaining 90 patients are not given, since there was a random distribution both of the averages and ranges of the values in any given patient whether or not he was receiving maintenance doses of *folia digitalis*. Sixty-five of the 100 patients studied developed congestive heart failure requiring hospitalization while being studied, but the levels of the selected objective criteria of decompensation rarely indicated its approach.

We feel that our data substantiate the impression that these criteria are indicative of the presence of heart failure only when the process is well advanced. If repeated, or continuous, measurements of the venous pressure, circulation time and vital capacity could be made, it is very likely that fluctuations betraying the approach of congestive heart failure would be observed. Once congestive heart failure has been established, all or most of these measurements do indicate the presence and relative severity of the process. However, our data lead to the conclusion that if these measurements are made at intervals they are relatively crude methods for evaluating the approach of congestive heart failure. Our findings might indicate that the process (congestive heart failure) developed and became established during the time interval between the taking of the last measurements and the admission of the patient to the hospital. However, several of the patients studied were admitted to the hospital only two or three days after relatively normal readings had been obtained in the clinic, but at the time of admission were found to have sustained high venous pressures, prolonged circulation times and low vital capacities with physical findings of moderately advanced congestive heart failure. Whether or not repeated measurements made during the week prior to admission to the hospital might have revealed the onset and progression of congestive heart failure is a question which can be settled only by more extensive investigation. In the light of present evidence, an affirmative answer does not appear unlikely.

Several points of interest with reference to the circulatory measurements obtained were noted. As reported by Peabody<sup>3</sup> and confirmed by others,<sup>4</sup> patients with heart disease who are not in failure have, on the average, lower vital capacity and longer circulation time than do "normal" individuals of the same age group. This was confirmed in our study. The highest values in the "with digitalis" column were not necessarily obtained during the first week or two following the administration of digitalis and no consistent curve could be plotted for any individual measurement over the period of observation.

Changes in weight appeared just as sensitive as the level of the venous pressure, circulation time, or vital capacity in evaluating the presence or

approach of congestive heart failure. The vital capacity was more sensitive in a few patients who developed predominantly left heart failure. With the possible exception of changes in vital capacity and weight, detailed questioning of the patient with regard to dyspnea, orthopnea, and transient ankle edema, together with a careful physical examination, were more reliable in evaluating the state of the circulation than repeated measurements of the circulation time, venous pressure or heart size.

In 27 patients, measurements of the transverse diameter of the heart were made during the period of maintenance dosages and during the times when digitalis was withheld. Frank decompensation was not present when these teleoroentgenograms were made and no significant differences in the heart size could be detected in the group as a whole, as brief study of table 2 will

TABLE II

Comparative measurements of the transverse diameter of the heart, derived from six-foot teleoroentgenograms, are shown. Note the lack of significant differences in this measurement during the two periods of observation. See text.

Pt.	Transverse Diameter of the Heart in Cm.		Pt.	Transverse Diameter of the Heart in Cm.	
	Without Digitalis	With Digitalis		Without Digitalis	With Digitalis
1	15.2	15.2	15	16.2	21.1
2	14.4-13.9	17.4	17	16.8	16.3
4	14.7-14.9	14.1-14.3	20	14	13.3-13.5
5	14.5	14.9-13.9	22	13.6	14.9-13.4
6	13.5	13.0	23	17.8-17.7	18.5
7	18.1-17.2	18.2-16.8	26	19.5	19.6-19.4
8	15.3	15.7	27	18.3-16.3	17.0-15.7
9	14.0	13.2	29	13.7	13.2
10	15.5	15.0	30	12.5	14.5-14.1
11	16.1	17.1	31	15.1-14.3	14.8-14.1
12	16.0-15.2	15.4	32	16.1	15.4
13	15.1	16.4-15.5	33	16.2	15.7
14	22.1	19.9	34	15.3	13.9
			35	15.1	15.5

show. Stewart<sup>5</sup> demonstrated that the diastolic heart size decreases when the patient with congestive heart failure recovers and LaDue and Fahr<sup>6</sup> have shown that the decrease in diastolic heart volume is progressive during the period of compensation. It is also known that digitalis will diminish the diastolic heart size of the normal heart,<sup>7</sup> but it is not known how long this effect persists. Our data can only be interpreted as signifying that maintenance doses of *folia digitalis* given to patients who have had congestive heart failure fail to produce permanent and significant changes in diastolic heart volume once compensation is established.

The number of admissions to the hospital during the time when *folia digitalis* was withheld was 45, but was only 20 during the period in which patients were taking maintenance doses of digitalis. Because of uncontrollable factors, the differences in the number of hospital admissions while under study cannot be evaluated statistically but may have an intrinsic significance,

since more than twice as many patients developed congestive heart failure during the period without digitalis.

Patients taking maintenance doses of digitalis had fewer subjective complaints and said they were able to "do more" when they were receiving the drug, although evidence of this nature is highly unreliable because of the psychic and willful improvement that may have resulted from the fact that the patient was receiving medicine.

### DISCUSSION

Our data suggest that the vital capacity, circulation time, venous pressure and weight are, at best, crude measurements of cardiac reserve and are less reliable in evaluating this important factor than a careful consideration of the symptoms and signs presented by a patient with heart disease. However, this in no way detracts from the value of these measurements in the study or evaluation of the degree of congestive failure present and of the mechanisms involved in the production and disappearance of cardiac decompensation.

The evidence presented here of the efficacy of maintenance doses of *folia digitalis* in preventing the recurrence of congestive heart failure, although not clear-cut, suggests that it may be desirable to keep patients who have had congestive heart failure on maintenance doses of *folia digitalis*, since the rate of recurrence is twice as great when the drug is withheld.

In another study<sup>8</sup> it was shown that once congestive heart failure is present the need for digitalis is increased. Six of the 20 patients who were readmitted to the hospital in congestive heart failure while taking 0.1 to 0.3 gm. of *folia digitalis* were given 0.8 to 1.6 mg. of lanatoside C intravenously with evident improvement. This suggests that frequent reevaluation of the therapeutic level of digitalization is indicated. We discontinue digitalis for three weeks at six month intervals and then redigitalize the patients with regular sinus rhythm and place them on a maintenance dose of *folia digitalis* of from 0.1 to 0.3 gm. daily.

### CONCLUSIONS

1. Of the 104 cardiac patients studied, 45 were admitted to the hospital for recurrent congestive heart failure during a test period in which *folia digitalis* was withheld. However, there were only 20 admissions during a period in which these same 104 patients were taking maintenance doses of *folia digitalis*.

2. The transverse diameter of the heart is not appreciably affected by the taking of *folia digitalis* over a period of two to 24 months, in the fully compensated patient with heart disease associated with regular sinus rhythm.

3. Patients with heart disease have a definite diminution in the vital capacity and a prolongation of the circulation time even in the absence of congestive heart failure.

4. Measurements at frequent intervals of the vital capacity, circulation time, venous pressure and weight failed to demonstrate the efficacy of maintenance doses of *folia digitalis* significantly to improve the cardiac reserve of patients with heart disease associated with regular sinus rhythm.

5. Maintenance doses of from 0.1 to 0.3 gm. of *folia digitalis* should be given to patients with heart disease associated with regular sinus rhythm.

6. None of the criteria employed in this study gives any accurate appraisal of the proper maintenance dosage of *folia digitalis* for patients with heart disease associated with regular sinus rhythm.

### BIBLIOGRAPHY

1. WITHERING, W.: An account of the foxglove and some of its medical uses; with practical remarks on dropsy and other diseases, 1785, M. Swinney, Birmingham.  
MACKENZIE, J.: Digitalis, Heart, 1911, ii, 273.  
EGGLESTON, C.: Clinical observations on the duration of digitalis action, Jr. Am. Med. Assoc., 1912, lix, 1352.  
EGGLESTON, C.: Digitalis dosage, Arch. Int. Med., 1915, xvi, 1.  
PARDEE, H.: Notes on digitalis medication. 1. The rate of disappearance of digitalis from the body. 2. The therapeutic dose of tincture of digitalis, Jr. Am. Med. Assoc., 1919, lxxiii, 1822.  
ROBINSON, G.: The rapidity and persistence of the action of digitalis on hearts showing auricular fibrillation, Am. Jr. Med. Sci., 1920, clxx, 121.  
CUSHNY, A.: The action and uses of digitalis and its allies, 1925, Longmans, Green and Co., London.  
GOLD, H., and DEGRAFF, A.: Studies on digitalis in ambulatory patients. II. The elimination of digitalis in man, Jr. Clin. Invest., 1929, vi, 613.  
GOLD, H., and DEGRAFF, A.: Studies on digitalis in ambulatory patients. IV. Newer principles in digitalis dosage, Jr. Am. Med. Assoc., 1930, xcvi, 1237.  
STROUD, W., and VANDER VEER, J.: A six year study of the clinical efficacy of various digitalis preparations, Jr. Am. Med. Assoc., 1937, cix, 1808.
2. KATZ, L., SOKOLOW, M., WEINBERG, H., and PLAUT, J.: Digitalis in the prevention of recurrent failure in patients with sinus rhythm, Ann. Int. Med., 1942, xvi, 427.
3. PEABODY, F.: Relation of the vital capacity of the lungs to the clinical condition of patients with heart disease, Jr. Am. Med. Assoc., 1917, lxxix, 1954.
4. KOCH, E.: Die Stromgeschwindigkeit des Blutes, Deutsch. Arch. f. klin. Med., 1922, cxl, 39.  
BLUMGART, H.: The velocity of blood flow in health and disease, Medicine, 1931, x, 1.  
BLUMGART, H., and WEISS, S.: Clinical studies on velocity of blood flow. XI. Pulmonary circulation time, the minute volume flow through lungs, and the quantity of blood in the lungs, Jr. Clin. Invest., 1928-29, vi, 103.
5. STEWART, H., DETRICK, J., CRANE, N., and WHEELER, C.: Action of digitalis in uncompensated heart disease, Arch. Int. Med., 1938, lxviii, 569.
6. LADUE, J. S., and FAHR, G.: The effect of the intravenous administration of Lanatoside C upon the output, diastolic volume, and mechanical efficiency of the failing human heart, Am. Heart Jr., 1943, xxv, 344.
7. BURWELL, C., NEIGHBORS, D., and REGEN, E.: The effect of digitalis upon the output of the heart in normal man, Jr. Clin. Invest., 1927, v, 125.
8. RAY, T., and LADUE, J. S.: The intravenous administration of Lanatoside C to patients taking maintenance doses of *folia digitalis* up to the date of hospitalization with recurrent congestive heart failure, Am. Heart Jr., 1945, xxx, 335.

# THE MEDICAL HISTORY: A SUGGESTED TECHNIC FOR INTERNISTS AND GENERAL PRACTITIONERS \*

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IN the light of the experience of those who, like Dunbar,<sup>1</sup> believe that many of the errors in medical diagnosis and treatment can be traced to the medical history, a review of the status of the medically acceptable case record should provide material which could be used for determining some of the sources of error and how they might be avoided or minimized.

Medical histories have been recorded since the beginning of history itself. Devotees left their stories on the pillars of the temples before Hippocrates braved the dawn of modern medical science, and down the centuries have come the complaints of suffering and the observations of physicians as to what morbidities were responsible for the clinical aspects of disease. The turn of the last century was marked by an era sometimes referred to as the "Golden Age of Bacteriology." Microbial causes of disease began to replace outgrown theories of etiology, and with contemporary contributions in the fields of chemistry and physics, better understanding of morbid anatomy, increased specialization among physicians, and general improvement in medical diagnosis, medical progress has contributed to the addition of a decade in life expectancy in less than 50 years. The present day method of taking case histories came into common use in 1902, when Cabot<sup>2</sup> instituted the case record method of teaching, in contrast to the more arbitrary intuitive art of his time. His clinicopathological conferences were innovations, and for several years printed reports of these sessions were widely distributed by subscription among the medical profession. In 1906, Barach<sup>3</sup> described an observation chart to supplement the hospital records which then were commonly limited to a graphic chart with or without a separate page for doctors' orders. His chart provided a single line for the daily record of hospital occurrences, treatments, and results. He remarked, "As time goes on and medicine becomes more of a science and less of an art, the better for medicine, as empiricism is being replaced by a sound principle, we find that system is more and more essential and detailed records must be kept and preserved."

In more or less discriminating circles, the pattern of the modern medical history is relatively uniform. It includes, first, the patient's chief complaints: namely, the symptoms which bring the patient to seek medical care, how long they have existed and how they began. Next comes a supplemental organ system review with the idea of gaining more detailed information about the nature of the complaints and bringing to light any the patient

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has overlooked. Also included are statements concerning previous illnesses and the dates of their occurrence; then, the family history referable to the ages, health, and causes of death of near relatives, and finally, a social history which is limited to brief statements of the patient's age, intellectual level, birthplace, habits, and economic and social status. Whether or not this order is followed, the material represents what is usually required from the patient when he presents himself for examination at the hospital, clinic, or the office of his physician. It is not a history in the sense that it is a record of events according to their relationship or sequence, subject to review and analysis as documentary evidence, but is a collection of data, concerned primarily with what might be revealed by physical examination or laboratory means. As a corollary to such clinical findings, its importance as a diagnostic instrument varies according to the nature of the medical problem. It has been conservatively estimated that probably 50 per cent of the cases in general practice are specific short term disabilities requiring little more than the evaluation of objective symptoms for their identification. In such instances, a personal history might contribute little to the diagnosis of the condition for which the physician is consulted and be of only relative importance in matters of treatment. But at least 50 per cent of the general practitioner's patients, and a far greater proportion of the internist's, present multiple cumulative complaints, among which are the overlooked or forgotten past illnesses, undiscovered pathological processes of the present, and the so-called "functional" complaints, more critically designated "autonomic nervous system disturbances," where symptoms are often protean in character and where there may be functional abnormalities in blood pressure, basal metabolism, glucose tolerance, gastrointestinal functions, etc. Left to the interpretation of subjective symptoms listed in the usual case history on the basis of physical and laboratory examinations or the intuitive assumption of psychoneurotic content, one is sometimes faced with a dilemma from which escape may be found in over-emphasis of non-consequential findings. Should reference to a psychiatrist be made another history must be taken which has the effect of detaching the emotional factors from other elements in a diagnostic problem. Such situations, from which none are immune, provide adequate reason for us to contemplate the criticism directed to our methods of history taking.

Before considering in some detail the possible sources of error in diagnosis which might exist in the medical history it is suggested that three common faults may be found:

*First:* The time allocated to the patient's recital of complaints may be insufficient to allow clarification.

*Second:* Difficulty of integration of subject matter exists when symptoms are separately grouped by organ systems without reference to relationship or sequence.

*Third:* Limitation of the personal history to more or less abstract and

relatively unimportant items omits information essential to the identification of emotional causes of somatic complaints.

Errors attributable to the length of the interview may be found in the time-saving categorical question and answer technic, notably in regard to previous illnesses and chronic diseases. Categorical questions are frequently difficult to answer and often carry suggestions that will influence the replies. In prolonged illnesses, particulars relative to chief complaints and other symptoms may be influenced by the patient's previous medical experiences, conversations with family and friends, to say nothing about what they have learned from the newspapers, radio, and periodicals devoted to matters of physical and mental health. Their social, economic, and intellectual status color their statements, and emotional factors, notably elements of fear, anxiety, and hostility, which become part and parcel of every chronic illness, may disguise a simple syndrome of organic disease or constitute a syndrome of their own. Sometimes deliberate misstatements are made, and apparently for as many reasons as there are vagaries in human character.

The inclusion of information of past and present symptoms in the record of chief complaints and their subsequent grouping by organ systems without regard to relationship or sequence render their integration difficult in proportion to the number and variety of items to be considered. Accepting the validity of all assembled data, organization is often impossible and an intelligent review or summary frequently cannot be made.

An ever present source of error exists in the lack of material concerning the patient himself: how he acts when under stress; what physical symptoms he has when agitated or on trial; what handicap, physical or otherwise, he thinks he has for attainment in family, business, religious and social circles; what he thinks of himself as a person. This lack of material may more subtly interfere with the accuracy of interpretation by influencing the examiner to identify himself with the patient's emotional problems. It is easy to evaluate another person's difficulty in the light of one's own experiences, and too much attention can be focused upon immediate situations without an understanding of what personality factors and circumstances may have contributed to them. It may lead to supplementation of information given by the patient with or without his consent by interviews with members of his family or associates which may add to confusion unless they are for specific incidents or circumstances in the history that need verification. Unless the examiner is aware of these influences he may find himself in the position of being led rather than leading in his efforts to be of service. Years ago Cannon<sup>4</sup> described the physiological reactions to hunger, pain, fear and rage, but their importance in the syndrome of disease cannot be determined if no reference is made to them in the medical history.

With these facts in mind, it is obvious that our method of history taking has not kept pace with other medical achievements of the past half century. It remains in form and substance, with few additions and refinements, what

it was when the chief concern of hospital staffs was the frequent discrepancies between antemortem and postmortem diagnoses. We now have reached the point where, with the aid of roentgen-ray and clinical instruments of precision, these discrepancies are the exception rather than the rule, and emphasis is being forced increasingly upon functional rather than anatomical abnormalities. We are not satisfied to know only that an individual has organic heart disease but how he can live usefully and comfortably with it. The psychic factors in such illnesses as allergies, diabetes, hypertension, and arthritis assume more important rôles, not only in their management but in etiology, and the only means available to determine how much importance is to be accorded them in individual cases is an adequate medical history. It is not so much a matter of differentiating between organic and functional disorders as it is determining all the factors of a patient's disability.

In answer to the pertinent question as to what might be called an adequate history, Cobb<sup>5</sup> states, "The point is to get the story of the patient's present predicament as much in his own words and his own order as possible. If this is done it is much more likely to be true than a story elicited by a set of stock questions. Many neurotic patients, when put through the mill of a regular routine: 'Chief complaint, present illness, past history, occupation history, marital history, system review and habits' will react badly and say things that they do not mean, some of them actually untruthful and misleading. To get all this down in the record is harmful because it not only wastes time but biases later opinion."

For the past two years an attempt has been made by the writer to evolve a case record technic in which the patient's history would rank at least as high in intelligibility as its other parts. First, the patient is allowed to state his complaints in as much detail as he desires in his own words with interruptions only to keep him on the theme of his *present illness*. When his statement has been completed, information relative to *present* functions of the neuro-muscular, cardio-respiratory, gastrointestinal and genito-urinary tracts is elicited as necessary to supplement what he has given. Following this recital of his present complaints, he is asked to give in his own words his personal history beginning with childhood. With the information that most chronic illnesses, functional and organic, have their origins in the easily forgotten past, he is told that the history might be given in narrative form so that, through association, as many of the events of his life as possible can be brought into the picture. No attempt is made to make him disclose what he might choose to leave unsaid, but the information desired concerns his childhood experiences and illnesses; his status in home and at school; the social, economic, and medical status of his parents and his preference for either one; how he reacted to disappointments and affection; what progress he made in school; how and when he learned about sex and what was his reaction to this instruction. He is encouraged to tell about his love affairs, religious experiences, ambitions, etc., as he passed through adolescence, and, when adulthood was reached, about his economic, social, and marital life

as it had been lived up to the time of the consultation. His own and his family's illnesses are placed in their proper setting as the story is told. The objective is to get as complete a summary as possible of all the elements that might enter into the complaints that bring him to the doctor's office. The interview is kept on a voluntary level and the benefit frequently derived is not only a mutual better understanding of the causes of presenting symptoms and a basis for future additions to the story, but where the beginnings of hypertension, allergies, and other chronic diseases can be placed in their proper setting, a workable program of treatment can be set up with less difficulty than if a narrative history is not secured. Where there are major psychic factors beyond the internist's capacity to handle, reference to a psychiatrist can more easily be made. The time taken for such histories has averaged 30 minutes to one hour. The patient having an objective and the opportunity to achieve it has less incentive or inclination to ramble.

The practical application of this method of history taking in general practice may be illustrated by the following abstracts:

#### CASE REPORTS

*Case 1.* A 23 year old white male employed as a gang foreman by an insulating company complained of periodic attacks of chest pain and shortness of breath which began a year before and had been increasing in severity and frequency for the past five months. In the past week, he had three severe attacks while at work filling the walls of houses with insulating material and had to be taken home. A roentgenogram of his chest was taken and he was told his lungs were "full of wool." He also complained of a pain in his left eye and loss of libido.

He was born on a farm, the second of four brothers and sisters. His parents were easy going church people and he was equally fond of both. He had measles, mumps, and chicken pox before 11 years of age and German measles at 14. One day, when he was five years of age, he and his cousin were testing their eyes at play and he found he could not see as well with his left eye as with the right. This frightened him, and his parents took him at once to an eye specialist in a nearby small city who put "drops" in his left eye and made him wear colored glasses for several days. Thereafter, three or four times a month, for six years, this treatment was repeated. He liked the doctor, who gave him ice cream, but did not like to wear colored glasses because he could not read for several days after each treatment. One day he heard the doctor tell his father that he had an abscess behind his left eyeball. The boys at school teased him because of his glasses and he was three years getting around to taking care of his tormentors. When he was 11 he was fitted with glasses, the left one as "strong as his father's reading glasses." His doctor died and he wore the glasses until he "outgrew them." Later he went to another doctor in the same town who gave him a new pair. He did not wear his glasses all the time but needed them when he was tired or upset about his studies. He was very much interested in church and took part in all of its activities. He masturbated occasionally until he was 18. Then one night he had a date with a young lady who had a reputation among the boys. On their way home he saw two people crossing a bridge in front of them and he thought they were his father and mother. Thereafter, he had no sex affairs and stopped masturbating. After graduating from high school he worked with his father at home and noticed that when he was working in a dusty place his nose would stop up but he did not have any symptoms of asthma. A year later he got a job with his present employers and married a girl from his home town whom he

had known since childhood. They had been happy, had one child, and he had made a good living for his family. He had enjoyed his work which had been the same for the past two years. He first was directly associated with a member of the firm of whom he was very fond. When this person took over another part of the business out of town, he was assigned to work under a man with whom he soon began to have trouble about his pay. Then he noticed that he would tire easily and had times when he got out of breath easily and his eyes bothered him. For five months there had been several occasions when he did not get all the pay for overtime to which he thought he was entitled, and two weeks later he worked 13 hours overtime and was paid for only five. This resulted in an altercation with the department head which almost ended in fisticuffs. He did not want to say anything or do anything "unbecoming a gentleman" or tell his troubles to anyone except the member of the firm who was out of town. He felt that his boss was dishonest in other matters also, and, if given time, would eventually be found out.

His attacks of pain and dyspnea became very severe and occurred every day or two. The pains were sudden in onset, making him stay in one position and hold his breath. They lasted from one to five minutes—always localized in the anterior portion of his chest. They were knifelike in character, gradually subsiding and leaving him weak, dizzy, and sometimes nauseated. For several hours afterward, he was exhausted and nervous and unable to work. He had always worn a respirator at work. During this period he had difficulty getting to sleep at night, his appetite was poor, and he had contemplated consulting a physician because of loss of libido. His eyes throbbed when he read too long and he went to the city where he was first treated for a pair of new glasses.

A roentgenogram of his lungs showed heavy bronchial markings but no parenchymal change. Roentgen studies of his gastrointestinal tract showed moderate hypermotility but no evidence of diaphragmatic hernia or other disease. Physical and laboratory examinations were negative except for amblyopia and a positive intradermal test with dust extract.

He was advised to have a talk with the senior member of his firm who had sent him for his examination and who later transferred him to work with another man. In a few days he was free of pain, had no difficulty eating or sleeping, and his marital affairs gave no grounds for complaint.

*Case 2.* A young man of 21, a third year college student, complaining of rapid heartbeat and abdominal distention presented himself for a "check up." He stated that he had always been under a doctor's care because of a "heart condition."

He was the youngest of two sons in a prosperous family and had a normal social life at home and at school. His father had some sort of "heart trouble" ever since he could remember. He never saw him in any acute distress but said his father was a person who kept his troubles to himself. His mother was always solicitous about the health of the members of her family. He had the usual diseases of childhood and a tonsillectomy at six years of age.

From two to 11 years of age he lived in a small town and during one of his illnesses the doctor found a "murmur" when examining his heart. Thereafter, whenever the doctor saw him the doctor would stop where he happened to be, at home or elsewhere at play, and listen to his heart. He was always cautioned by the doctor and his mother to "take it easy."

He had no other illnesses but went occasionally to a doctor for "check ups." Each time he was told to "take it easy" and not get tired, and when a college physician told him he was in good health he felt that the doctor knew he wanted to go to college and would not stop him even though he had "a heart condition." He was examined for R.O.T.C. and later passed the army induction center where he thought the examiner was inexperienced and did not give him as careful an examination as

would a more competent man. His social history indicated no abnormalities and he stated that the only stress he had experienced had been his anxiety about his "heart condition" which he said he took as philosophically as possible and if he died of heart disease he "would not be any worse off than a great many others with the same trouble." However, he did not want to "do anything foolish" that might make his end come sooner than necessary.

He noticed that his heart beat rapidly during and after exercise and occasionally when lying quiet he had a "spongy feeling" in his precordium where there was also an occasional slight pain or "catch." After climbing a long flight of steps he became aware of a forceful pounding which subsided in one or two minutes. He had taken part in sports but always had been conscious of his heart and when it pounded forcibly he had always stopped what he was doing. He said he did not want to take a "morbid view of his incapacity." He also noticed that immediately after eating his abdomen became distended and he passed a great deal of gas by belching and by rectum.

Physical and laboratory examinations revealed no abnormalities and exercise tests were normal.

When it was pointed out to him that his heart behaved like the hearts of other men, he asked why then had he been told to "take it easy." Later he got assurance by comparing his heart action with his roommate's and doubted less the ability of the college and army physicians to identify heart disease.

These two cases illustrate the part played by early childhood experiences in the development of inadequate personalities. In the first case, the boy was handicapped for six years in his studies and in looking out for himself with his schoolmates. Thereafter, when in trouble, his attention became focused upon his physical disability and he retreated into a mild form of invalidism. When he grew up he had not learned to deal with adult problems and his autonomic nervous system response to stress was exaggerated to the point where it contributed to an incapacitating illness. In the second case, the young man in early life had been encouraged to identify himself with his father, who was said to have had heart disease, by repeated examinations of his own heart and the guarded solicitude of his mother and examining physicians. In neither instance could the most noteworthy factors in etiology have been brought to light by the customary methods of history taking.

The cases are presented for the single purpose of illustrating how the correlation of physical symptoms and emotional equivalents in a narrative medical history may give the general practitioner a serviceable instrument in physical diagnosis. It is not to be inferred that the subject matter of such histories includes all the information that is necessary for psychiatric care.

#### BIBLIOGRAPHY

1. DUNBAR, FLANDERS: Psychosomatic diagnosis, 1943, Paul B. Hoeber, Inc., New York.
2. GARRISON, F. H.: Introduction to the history of medicine, 1929, W. B. Saunders Co., Philadelphia.
3. BARACH, JOSEPH H.: An observation chart, New York Med. Jr., 1906, lxxxiv, 339.
4. CANNON, W. B.: Bodily changes in pain, hunger, fear and rage, 1929, D. Appleton & Co., New York.
5. COBB, STANLEY: Technic of interviewing a patient with psychosomatic disorder, Med. Clin. N. Am., 1944, xxviii, 1210-1216.

# ANALYSIS OF ROENTGEN-RAY DIAGNOSIS IN CARCINOMA OF THE CECUM AND ASCENDING COLON \*

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## INTRODUCTION

THE value of roentgen-ray study in the diagnosis of carcinoma of the colon is well established. Clinicians have noted that a barium enema done routinely may reveal a carcinoma, even though the patient has no symptoms of a malignant lesion. On the other hand, there is a tendency to allow a negative barium enema report to rule out carcinoma of the colon even in the presence of suggestive clinical findings such as change in the bowel habit, abdominal pain, anemia, weight loss, fatigue, the presence of a mass, etc.

Hodges<sup>1</sup> states that the "x-ray manifestations of colonic neoplasm can be misinterpreted even by experienced observers trying diligently to make correct diagnoses." Bockus<sup>2</sup> states that "lesions in the flexures of the colon and those on the posterior wall of the caecum are liable to be missed" and that one should "studiously avoid a sense of false security given by negative reports made following barium enema study, particularly when there are clinical indications of malignant disease of the colon." Feldman<sup>3</sup> states, "In doubtful cases it is important to carry out repeated roentgen studies." The purpose of this paper is to evaluate the barium enema findings in the diagnosis of carcinoma of the cecum and ascending colon.

Whitehead<sup>4</sup> calls attention to the fact that one should resort to very careful fluoroscopic examination and frequent spot films to improve the accuracy of the diagnosis of carcinoma of the colon. Weber<sup>5</sup> emphasizes the importance of proper preparation of the patient before barium enema and advises double contrast examination. Schätzki<sup>6</sup> calls attention to the difficulty of differentiating diverticulitis from carcinoma of the colon and the importance of preservation of mucosal folds in making the differentiation. Case<sup>7</sup> cautions against overfilling of the terminal ileum, since, with overfilling, coils of the ileum may interfere with the post-evacuation study. He also states that a well-trained and experienced roentgenologist should succeed in identifying malignancy of the colon in 90 per cent of the cases. Morrison<sup>8</sup> advises that in order to continue below a 10 per cent failure in roentgen-ray diagnosis, the radiologist should be given a complete history by the physician. He also states that adequate preparation is imperative and re-

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peated examinations should be made if symptoms persist after a few weeks of treatment.

Because of the peculiar anatomy and character of pathological changes of the cecum and ascending colon, several facts concerning roentgen-ray diagnosis of carcinoma of the cecum and ascending colon should be noted. First, since the cecum is most distant from the anus, the cleansing enema is less apt to be effective in preparing the cecum than in preparing the rest of the lower bowel. Second, the cecum and ascending colon are larger in diameter than the remainder of the large intestine. Because of this fact, a lesion in the cecum or ascending colon does not usually produce obstruction as early as a malignant lesion elsewhere in the large bowel. This lack of evidence of obstruction makes the diagnosis more difficult. Third, because of the size of the cecum and ascending colon, it is easier to overlook a filling defect here than in the rest of the large intestine. This is particularly true when the filling defect is on the posterior wall. Fourth, carcinoma of the cecum or ascending colon is apt to be polypoid, producing late symptoms, signs, and roentgen-ray findings. In summary, carcinoma of the cecum and ascending colon are usually more difficult to diagnose by barium enema studies than carcinoma of the more distal lower bowel.

#### METHOD

All roentgen-ray examinations were done by the personnel of the Roentgenological Department of the Henry Ford Hospital. The patients were prepared for examination by purgation with castor oil the evening before, and by taking a saline enema the morning of the examination. It was a routine procedure to do a careful fluoroscopic examination before taking the barium enema film. Spot films and double contrast films were done in some cases and evacuation films in others. All cases included in this study proved to have carcinoma of the cecum or ascending colon by biopsy studies at operation.

#### RESULTS

The time interval between examination and operation is important. Of the four negative examinations, all examinations were done within six weeks of operation. Of the eight cases requiring two examinations, in two cases the first examinations were done six and seven months prior to operation; in the remaining six cases, the first examinations were done within one month of operation. In the two cases requiring three examinations, in one case the examinations were done six weeks, two weeks, and five days before operation; in the other case, examinations were done six months, five and one-half months, and one week before operation.

Table 1 shows that the diagnosis was made on the first roentgen-ray examination in 36 cases. Repeated examinations were done upon 10 cases either because the first examination was unsatisfactory owing to poor prepa-



TABLE I  
Diagnosis of Carcinoma of the Cecum and Ascending Colon from Barium  
Enema Examinations

	Number of Cases
Diagnosis of organic lesion on first examination	36
Diagnosis of organic lesion on second examination	8
Diagnosis of organic lesion on third examination	2
Negative examination	4
Poor preparation, not repeated	2 *
Total number of cases	50

\* In these two cases no diagnosis was made because of poor preparation and the Roentgenological Department suggested repeat examinations. However, the clinical findings and urgency of operation prevented this. Since the barium enema examination was not satisfactory and repeat examination was recommended, these two cases are not included in our percentages.

ration of the patient, or because the clinical findings were so suggestive of a malignant lesion that the clinician was not satisfied with one negative roentgen-ray report. On the repeat examinations, the malignant lesion was diagnosed in these 10 cases. Consequently, roentgen-ray examination was diagnostic of an organic lesion of the cecum and ascending colon in 46 out of 50 cases, or 92 per cent, of carcinoma of the cecum and ascending colon. Two patients operated upon before repeat barium enema examination could be carried out are not included. Table 1 illustrates the importance of repeating the examination when the patient is poorly prepared, or when the clinical signs are suspicious of a malignant lesion of the cecum and ascending colon. It also shows the importance of close liaison between the roentgenologist and the clinician.

Careful coöperation between the clinician and roentgenologist is of great value in arriving at a successful diagnosis and in determining when a repeat examination should be done in the event of a negative report. The two cases in which the examinations showed only poor preparation might have shown the malignant lesion with repeat examination after better preparation of the patient.

Some of the examinations reported in table 1 were done before the use of evacuation and double contrast films and spot films. It is believed that these new technics should improve the accuracy of diagnosis of carcinoma of the cecum and ascending colon.

TABLE II  
Type of Defects Found on Barium Enema Examination in Carcinoma of the  
Cecum and Ascending Colon

	Number of Cases
Total number diagnosed	46
Filling defect	32
Irregularity	24
Narrowing of lumen	8
Obstruction to barium	7
Small bowel obstruction	6
Intussusception	1

Negative examinations were obtained in four cases. One of the four cases had two barium enemas because of the strong clinical impression of malignancy of this area. In one of the four cases a diagnosis of an extrinsic lesion deforming the cecum was made. The error in diagnosis was less than



FIG. 1. Barium enema of carcinoma of the cecum showing filling defect in the cecum.

10 per cent and corresponds generally with the margin of error observed elsewhere in the diagnosis of carcinoma of the colon. We believe that an 8 per cent error in the diagnosis of a malignant lesion of the cecum or ascending colon is fairly low.

From table 2 it is apparent that a filling defect was present in 32 cases

and was the most common roentgen-ray finding. Irregularity was present in 24 cases. Eight cases had a narrowing of the lumen, seven had obstruction to the barium, and six cases had small bowel obstruction. One patient had definite evidence of intussusception.

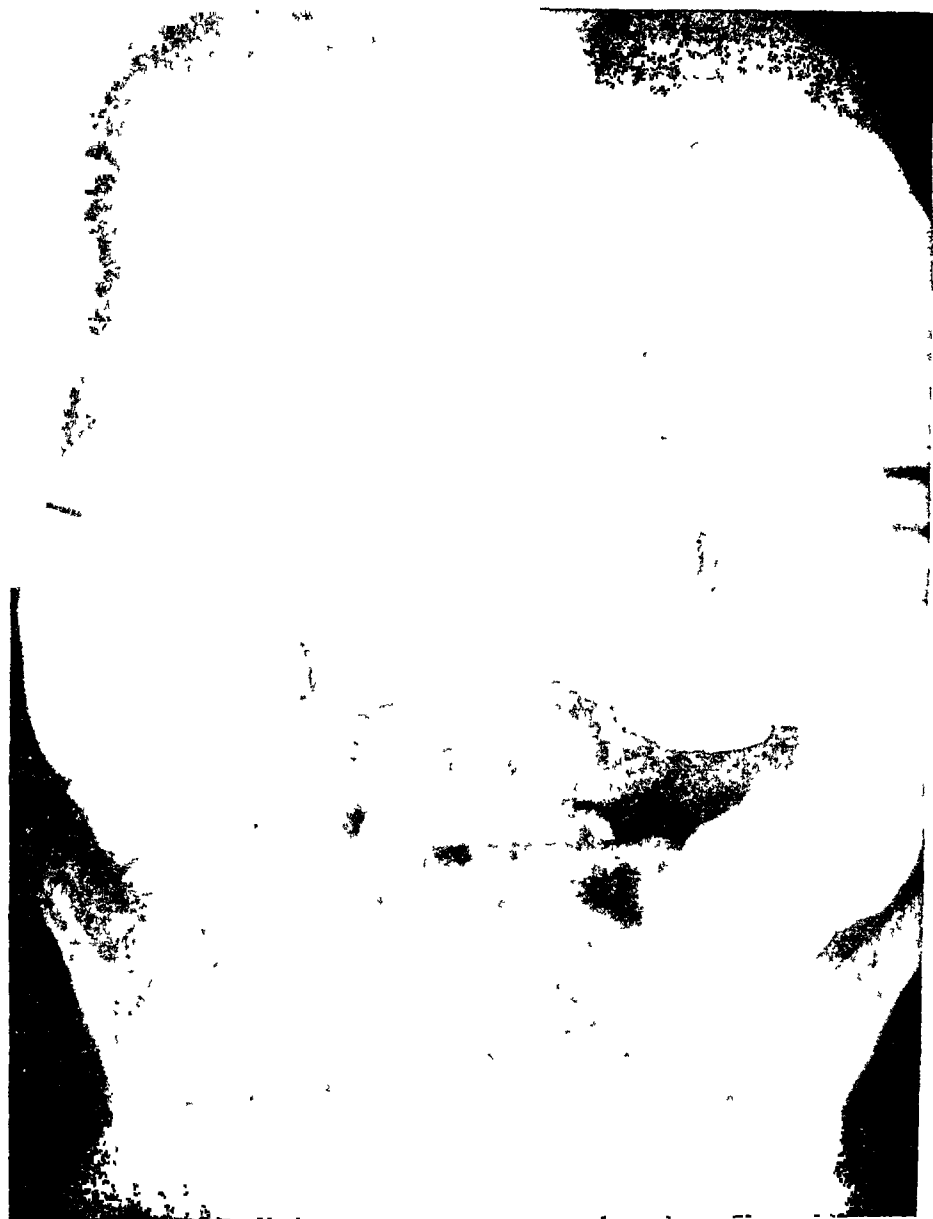


FIG. 2. Barium enema of carcinoma of the cecum showing filling defect, irregularity, and partial obstruction at the ileo-cecal valve.

Two cases were difficult to diagnose because the cecum was redundant and low in the pelvis, making palpation difficult. It is important that over-filling of the colon and ileum be avoided in the examination, since loops of the ileum then may obscure the cecum.

Examples of the type of defects listed in table 2 are seen in figures 1 to 4.

## SUMMARY

The barium enema examinations in 50 cases of carcinoma of the cecum and ascending colon, proved at operation by biopsy, were analyzed.



FIG. 3. Barium enema of carcinoma of the ascending colon showing narrowing of the lumen and a constricting lesion of the ascending colon.

The roentgen-ray diagnosis of carcinoma of the right side of the colon is more difficult than the diagnosis of carcinoma of the left side of the colon because (1) the cecum and ascending colon are more difficult to prepare for examination, (2) carcinoma of the cecum and ascending colon is less apt to produce an annular constricting or an obstructive lesion, and (3) because

the size of the cecum and ascending colon frequently makes it easier to overlook a small filling defect.

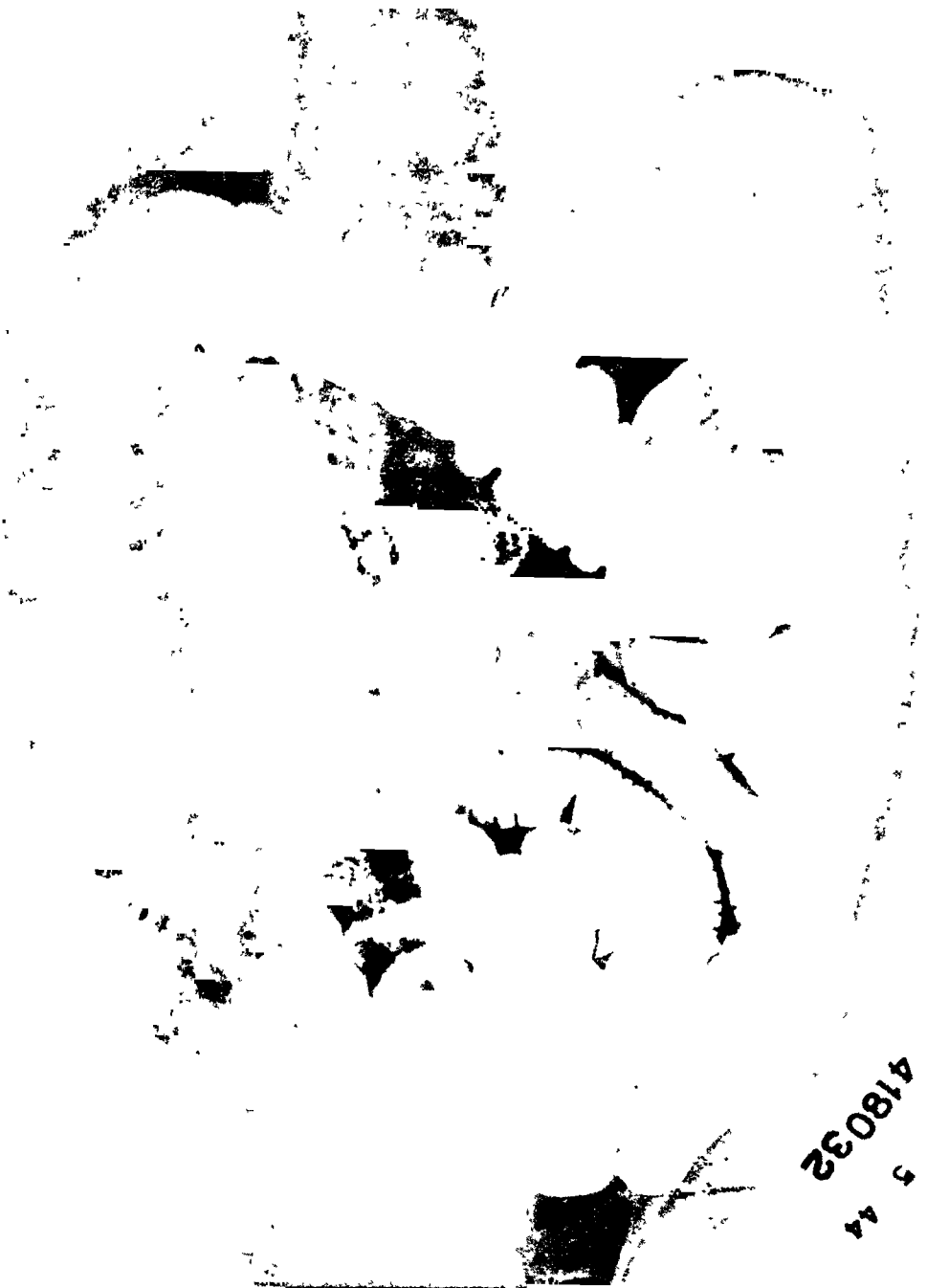


FIG. 4. Barium enema of carcinoma of the ascending colon showing narrowing and irregularity of the ascending colon.

Correct diagnoses were made in 36 out of 50 cases, or 72 per cent, on the first examination. Ten patients, or an additional 20 per cent, had to have a repeat barium enema before a diagnosis was made. The reason for

the repeat examination in some cases was poor preparation for the first examination; in other cases the repeat examination was done because of clinical evidence of a malignant lesion in that area. The patient must be well prepared for the barium enema study if carcinoma of the cecum or ascending colon is to be ruled out. Even with good preparation and a negative report, the examination should be repeated if there is any clinical evidence of a malignant lesion in this area.

With careful examinations, and repeat examinations whenever indicated, the error in diagnosis of an organic lesion in this area should not exceed 10 per cent. The barium enemas of four, or 8 per cent, of the proved cases of carcinoma of the cecum or ascending colon in this series of 50 cases were reported as negative for an organic lesion of the cecum or ascending colon.

The most common diagnostic roentgen-ray findings were filling defects and irregularities, which were present in 32 and 24 cases respectively. Narrowing of the lumen was present in eight cases, obstruction to the barium in seven cases, small bowel obstruction in six cases and one case had evidence of intussusception.

### CONCLUSIONS

Roentgen-ray diagnosis of carcinoma of the cecum and ascending colon is often difficult.

Good preparation for the examination is necessary. The examination should be repeated if there is any question about the preparation.

Even with good preparation and a negative barium enema study, the examination should be repeated if there is clinical evidence suggesting a malignant lesion in the area.

With careful technic and preparation, using fluoroscopy and films, and doing repeat examinations whenever indicated, the error in roentgen-ray diagnosis of an organic lesion of the cecum and ascending colon can be kept at 10 per cent or less.

### BIBLIOGRAPHY

1. HODGES, F. J.: The gastrointestinal tract (a handbook of roentgen diagnosis), page 208, 1944, Year Book Pub., Inc.
2. BOCKUS, H. L.: Gastroenterology, Vol. 2, page 765, 1944, W. B. Saunders, Philadelphia.
3. FELDMAN, M.: Clinical roentgenology of the digestive tract, 1945, Williams and Wilkins Co., Baltimore, page 769.
4. WHITEHEAD, L. J.: Roentgenological manifestations of malignancy of the colon, *South. Med. Jr.*, 1945, xxx, 85.
5. WEBER, H. M.: The roentgenologic demonstration of polypoid lesions and polyposis of the large bowel, *Am. Jr. Roentgenol. and Rad. Therapy*, 1931, xxv, 577.
6. SCHATZKI, R.: The roentgenologic differential diagnosis between cancer and diverticulitis of the colon, *Radiology*, 1940, xxxiv, 651.
7. CASE, J. T.: A clinical approach to the roentgen diagnosis of carcinoma of the colon, *Illinois Med. Jr.*, 1941, lxxx, 145.
8. MORRISON, L. B.: The rôle of x-ray in the diagnosis of carcinoma of the colon, *New England Jr. Med.*, 1930, cciii, 441.

# PROTECTIVE REACTION PATTERNS AND DISEASE\*

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AN ancient awareness of the linkage of feeling and bodily changes is borne to us in the heritage of our language. Applied to the vasomotor system we have such phrases as "red in the face," "hot under the collar," "pale with rage," "being in the pink of condition"; applied to respiration—"takes one's breath away," "sighed heavily with passion," "his nostrils dilated with rage"; applied to perspiration—"went into a cold sweat," "cold hands, warm heart," "he has cold feet," "dripping with suspense"; applied to the gut—"it's a nauseating experience," "it makes me sick," "it turns my stomach," "I can't swallow that," "it's a gripe." In Henry VIII, Shakespeare refers to Woolsey as a man of "unbounded stomach." When referring to a frustrating situation it is said in current slang, "it is a headache." We say, too, in reference to pilomotor functions, "his hair stood on end," "it made his flesh creep"; in reference to skeletal muscle—"he's a pain in the neck," "he trembled with fear," "he shook with rage," "he had jitters," "he's a stiff necked fellow," "he became weak with laughter," "keep a stiff upper lip"; as applied to cardiovascular apparatus—"faint heart ne'er won fair lady."

The relevance of such bodily changes to disease has been brought into focus only recently, mainly because it has not been clear that these functional alterations may be profound or sustained enough to be of clinical significance. But now such sustained bodily alterations connected with varying life situations and emotions have been observed and recorded and to consider their pertinence to disease and tissue damage is the purpose of this essay.

*Development of Concepts.* We have been encouraged by our teachers to abandon dualisms and dichotomies such as are exhibited when body and mind are used as opposing terms, and to develop a unitary concept of man. Such sound counsel has led to attempts at formulation, but our teachers have left us little data or language with which to proceed.

Darwin, Pavlov and Cannon attempted unitary concepts of behavior, but because of lack of information and tools, as well as because of the orientation of their times, the results, despite their importance, are limited. Thus Darwin, in his remarkable essay "Expression of Emotions in Man and Animals," has concerned himself relatively little with internal bodily reactions or with the analysis of drives. However, his detachment and curiosity about human behavior were a basic impetus to all later study. In tracing the humble origin of man and in discovering in his patterns of expression, links with his ancient past, he ploughed the ground for Freud.

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The demonstration by Pavlov that a given stress situation produces in the dog reactions of a highly individualized character based on the nature and experience of the particular animal, has had important implications for human behavior problems. Very significant, also, is the demonstration that such psychobiological stress can produce not only severe, but long lasting disorders of function.

The initial effect of Pavlov's data was an actual slowing of the progress of the study of man through the implication that it was unnecessary or even pernicious to use his own unique qualities of language and self-awareness. But soon it became apparent that sound scientific principles can operate in work with symbols as well as in experiments with more measurable components such as secretion and contraction. Thus, through the study of quantitative aspects of conditioned reactions in the dog, human behavior, hitherto considered "too complex" for the scientific method, became a subject matter for science.

Cannon had the courage and imagination to arrange the isolated and detailed phenomena of neurohumoral functions into an integrated pattern of emergency reaction, seen as mobilization of the animal's responses for fight or flight. Though this concept failed to distinguish between various kinds of protective reactions and took little account of varieties of feeling, it nonetheless emphasized the existence of a protective reaction pattern.

Exploring in other fields, Janet, Morton Prince, Freud, and Jung (notably Freud), formulated the concept of unconscious mental activities. Accordingly, the phenomena of mentation and behavior are conceived as the result of the interaction of a number of drives. These drives, which are in part conscious and in part unconscious, may work harmoniously together, or conflict with one another. In the latter case attempts at adjustment occur. Certain of these attempts involve the repression of one of the opposing forces, which then is no longer allowed to manifest itself in consciousness or in action. It becomes unconscious, but does not thereby cease to exist. It remains capable of functioning. It can no longer influence thought and behavior in a direct manner, but instead produces various indirect effects. This conception has illuminated our understanding of attitudes, feeling states, preferences, prejudices and decisions. But feeling states and behavior patterns were not correlated with other bodily reactions by these investigators.

Adolph Meyer, in the spirit of American pragmatism, saw man as a unit of function within the framework of general biology. No organism, he pointed out, is a mere accumulation of its component parts, but rather by virtue of complex interaction new potentialities occur, the nature of which can never be understood by analysis of the parts. Meyer taught that mental function, or mentation, is not to be regarded as a unique or detached process, but only as a special kind of functioning made possible by the particular integration of man's makeup; that man is a set of functions integrated into an adaptive unit called a "personality"; and that a discipline, which Meyer called psychobiology, could be developed which would study the human being



as a functioning entity. Meyer was primarily concerned with the shaping of his concept and only secondarily with the experimental demonstration of its fruitfulness. Hence his effort has influenced thought less rapidly than might otherwise have been possible.

At the moment, the bodily alterations connected with varying life situations and emotions are viewed in a variety of ways, each of which has its adherents. One is that the changes occurring in association with various feelings are meaningless, fortuitous, haphazard, and in a sense chaotic. They play no essential part in the reaction, but are seen as the outcome of a diffuse excitation within the central nervous system inducing effects in blood, smooth muscle, gland and skeletal muscle.

A second view presents the bodily alterations as manifestations of special anatomic peculiarities of the individual, and considers that certain individuals, during duress, incite activity within their sympathetic systems predominantly, whereas others do so within their parasympathetic systems. The responses are looked upon as resulting from excitation which, respectively, affects adrenergic or cholinergic fibers, but no other meaning has been imputed to these changes. This implication that a defect, either congenital or acquired, exists in one of the parts of the nervous system, giving rise to over- or under-activity, is akin to the view held by others that certain individuals are equipped with inferior organs which, under stress, break down, i.e., the stomach in dyspepsia. The defective functioning of the inadequate organ would thus add to the load put upon the man.

A third view (which to me seems more useful) looks upon the bodily changes occurring with various adverse life situations and accompanying emotions as not haphazard nor as evidence of organ inferiority, but as part of an arrangement or pattern, in which is integrated as much of the organism's equipment as is needed for a particular protective effort. It is implied that smooth muscle, gland and skeletal muscle functions, feeling states, attitudes and emotions are linked and have direction, although this direction may be at variance with the conscious purposes of the individual.

When assaults and threats are squarely faced by the individual, and elicit prompt action, the self-protective pattern in his behavior is clearly seen. Thus, a boy avenging an insult by hitting hard in fisticuffs uses a necessary part of his protective equipment to deal with the assault. Less obviously related to environmental stimuli are patterns of protection evoked unconsciously, when drives unacceptable to the individual are repressed. These drives may be touched off by symbols often unrecognized. For example, a man, after being subjected to a lifetime of destructive domination by his mother, cannot allow himself to strike her, nor even to feel anger toward her. An apparently neutral incident can arouse his hostility but his evoked anger is repressed. Such drives continue to affect behavior, but since they are barred from awareness, the protective patterns evoked may be only atavistically relevant to the situation. For instance, increasing the heart rate to improve circulation is a primordial response for fight or flight, but tachy-

cardia cannot regain love for a rejected spouse. Nevertheless, the protective patterns evoked may be specific in character, indicating efforts to get rid of, to shut out, to fight or to flee.

These patterns become medically significant when they are prolonged, since irreversible changes and tissue damage may ensue. Hence duration is of prime importance. When the individual's reactions are on the conscious level, his protective patterns serve their purpose and usually are promptly dissipated. However, under certain circumstances the need for them may be prolonged, as during exposure to sustained adversity or to a series of threats in battle. Also, because of unusual sensitivity based on special experience the individual may over-react to relatively minor assaults and thus protective patterns persist for long periods. Furthermore, when, due to conflict and subsequent repression, an individual's reactions are out of awareness, the unconsciously evoked protective patterns may persist as long as the repression lasts, which may be for years. The resultant picture is one of antagonistic purposes and contradictory behavior, since contrary drives are being expressed. Within each pattern, however, behavior and bodily reactions are consistent and protective in aim.

There are many such protective patterns, both defensive and offensive. It is likely that the neural processes involved in conditioned reactions are operating in these behavior patterns, but at the moment it is more profitable to consider behavior in broad biologic terms. Any one organ or system may participate in either defensive or offensive patterns. A few of these patterns will be touched upon here, and the first to be considered will be an offensive protective pattern, involving assimilation.

*Protective Patterns of Offense Involving Eating—the Stomach and the Duodenum.* Direct observations were made possible by Tom who came to us with a large abdominal stoma. This man, now 59 years old, came home one night when he was a child aged nine, thirsty and hot after playing in the streets. Finding on the back of the stove a large beer can filled with what he thought was cold beer, he grasped the beer can, took a large mouthful of the hoped-for cool, frothy stuff, but instead he had to swallow scalding hot clam chowder. During the next few months many attempts were made to expand his partially occluded esophagus, but with the passage of time it became apparent that this was not going to be possible. He was then brought to the hospital malnurtured and in terror.

The surgeon planned to make a small stoma through which to feed the child and ultimately to close the stoma after suitable arrangements had been made in the esophagus. For various reasons, however, the child did badly at the operating table, and the operation had to be hastily concluded. So instead of getting a small stoma, this child was left with a large opening and a generous collar of mucous membrane on the outside. This man grew up, worked, got married, had children, and conducted himself as a responsible citizen for the next half century. He is a shy, sensitive, lively little man, quick to anger, quick to forgive, unschooled, responsible, overly conscientious.

He became a diener in our laboratory and the plan was that he'd come in every morning without having breakfasted, put himself on a table, and allow us to look into the stoma. After preliminary observations the important events of the last 24 hours, his attitudes about them, whether things were going well at home, what his feelings were, would be discussed. Tom is a "man of few words" but he is nevertheless articulate in the sense that sooner or later you know exactly what he feels. He has the ability to communicate.

To round out a rather small salary, this man cleaned the apartment of a member of the medical school staff. Tom did not know much about cleaning apartments and he was slow, ineffective, and costly in terms of the help available at the time. So my associate planned to "fire" him. This was done under laboratory circumstances. When he discharged him, he told Tom about his deficiencies. Tom got red in the face, saying, "Yes, Sir," "No, Sir," not expressing his anger in words, but exhibiting it by color changes in his face and stomach. When my associate left, Tom was "boiling with anger" and said, "I could choke that man," as a final comment on the subject. During the words of dismissal, the gastric mucosa got red (increased blood flow), the hydrochloric acid secretion and motility increased.

Here, then, is a response of peptic hyper-functioning, with anger, conflict, resentment, which may last a matter of minutes or days or weeks. Usually Tom quickly "blows his top," and then his anger is ended. The situation may be sustained for a few days or weeks, however, and the stomach hyperfunction may be likewise sustained. Thus Tom had a benefactor who gave him a certain amount of money to round out his small income. Tom resented his benefactions because, like many benefactors, this one felt free to meddle in Tom's personal affairs and tell him how to spend his money. He was not being deprived of love or security, but was being deprived of exercising his right to live in his own way. Following a visit from his benefactor, the stomach had a high color and was hyperacid. This persisted for two weeks, and was dissipated by raising Tom's salary and enabling him to throw off his benefactor. Tom's gastric reaction to threats is characteristically one of hyperactivity, just as his way of meeting an adverse life situation was to take active steps to correct it.

When there is a high color in the exposed mucosa, the tissue bleeds easily, due probably to the increased fragility of the distended minute vessels. After sustained resentment, one may see many small hemorrhages, scattered here and there over a wet, hot-looking, shiny, engorged mucosa. When tranquility is reestablished and the situation is left to itself, the hemorrhagic spots spontaneously disappear although the mucosa may remain edematous for some days. If one interferes in any way with the protective action of the mucus, say, by removing the mucus and putting a little wall of petrolatum about such a spot and then allowing the gastric juice, with its hydrochloric acid and pepsin to act on the unprotected surface, an ulceration can easily be produced. However, when the mucus is again allowed to protect that area,

within three days there is no sign of a lesion. During the period of noxious stimulation of the mucosa by the action of the gastric juice there is a vicious cycle started in which both blood flow, color, and acid production are increased. So, once the lesion is started, a self-perpetuating cycle, due to the presence of the lesion and noxious stimulation, is established.

What has been observed in Tom is relevant to others. In a patient with peptic ulcer studied by conventional methods, we have seen various levels of gastric acidity at different times; a low level was associated with a period of relative security, a high one with extreme insecurity in which the patient was being pursued by the police. He is a professional beggar, and begging in this instance is part of a pattern of "getting even" with society for injuries that he sustained as a child and as an adult. He insisted on coming into the hospital via the private entrance and then coming up in the private patient's elevator. The doorman knew of our work with him and never interfered. However, on one particular day the patient found a stranger at the door, a substitute doorman who, not knowing our subject, sent him to the back entrance, so to speak, and up to our laboratory via the Out Patient elevator. The man entered the laboratory in a humiliated, angry state, and with a small amount of fresh blood in his stomach. This was appreciably increased during the interview about his recent experience. When, after a few minutes, the topic was rediscussed, bleeding was renewed. Whether this was bleeding around the already existing ulcer or the breaking up of a small blood vessel elsewhere in the now engorged mucosa, is not clear, but it is evident that this man's protective reaction to an adverse situation, like Tom's, includes the stomach.

Thus, one of the earliest aggressive patterns to manifest itself in the infant, namely, that associated with hunger and eating, may, in certain individuals, in later life, when the organism is threatened, reassert itself. At such times of anger, the feeling itself, the demand for emotional support or insistence on being cared for may be repressed by the equally insistent assertion that the individual is strong, independent, capable of doing alone, of standing on his own feet. Either through actual deprivation of support or an unwillingness to accept it, this angry, hungry state shows itself in the stomach as one of readiness for eating.

The hyperdynamic state of the stomach first becomes associated with symptoms arising from excess motility, engorgement and hyperacidity and this may be followed by damage of the gastric mucosa. It is the conflict between two goals, one not clearly stronger than the other nor yet in agreement. A conflict between two parts of a man expressing "I want" and "I won't let myself have," or "I want and I can't get it." The reaction pattern expresses divergent goals, now one now the other, sometimes both at the same time. The animal appears unable to resolve the dilemma created by his conflicting drives and in the struggle digests his own gut. In essence, the activities of this man in dealing with his day to day problems took the form of offense. Even though "an humble beggar," his aggressive acts took the

form of childish temper outbursts (perhaps because the infant is an angry beggar when hungry). It was possible to demonstrate in another fistulous subject studied before and after vagotomy that the vagus nerve was the principal neural pathway involved in vasomotor and motility changes associated with gastric hyperfunction during conflict and anger.

*Protective Pattern of Defense: The Ejection-Riddance Reaction Involving the Large Bowel, the Stomach and Duodenum.* Many infants during the onset of infection vomit and have diarrhea in reaction to the invasion of a noxious agent even when the gastrointestinal tract is not primarily involved. Hence, during a fretful, irritable, uneasy state the feverish infant attempts to protect itself by ejecting that which it has inadvertently admitted. Usually before adolescence the child abandons the non-specific and inappropriate reaction to assault, utilizing it sparingly to rid itself of noxious agents actually present in the gut. But some adults persist in the inappropriate use of the ejection-riddance pattern, even when the assault has nothing directly to do with the gut. A subject actively participating in the environmental demands made upon him, but finding himself inadequate to deal with them may elaborate a pattern of ejection. Thus, a person who has "taken on more than he can handle" or feels inadequate to the demands of his life situation, or a thwarted person filled with hatred, defiance, contempt and the unconscious aim to eject a threatening or overwhelming situation, may have diarrhea. However, the riddance pattern being integrated through unconscious processes, the subject exhibiting violent diarrhea may be calm, sweet mannered, and even serene.

Almy, studying subjects with hyperirritable large bowel and mucous colitis, found hypermotility and a bright red mucosa secreting excessive mucus. It would appear as though the large bowel functions under the circumstances of ejection in a manner different from that of the stomach. The latter is pale and hypomotile, though it contains much mucus. (S. Wolf).

Our subject, Tom, with the large gastric fistula, revealed that an agent such as ipecac which, because of its toxicity, threatens survival, or "Amigen" or "Amphogel" which because of their texture, taste or other unesthetic qualities were unacceptable or revolting, elicited anorexia, feelings of nausea, and often precipitated into action the duodenal and skeletal muscle patterns of vomiting. The motility and tone of the stomach diminished, the acid secretion dropped dramatically, and the gastric mucosa became pale. However, the mucus secretion increased, and subsequently vomiting occurred. Such an increase in mucus secretion is compatible with the view that the noxious agent might be diluted, neutralized, or washed away. This, coupled with a motor pattern which empties the stomach through the esophagus and mouth, would be maximally effective in protecting the organism against an ingested poison.

It also became evident that unacceptable or offensive situations, or those eliciting feelings of disgust, were likewise associated with sensations of nausea, increased secretion of mucus, and depressed digestive function.

Also with the increased mucus secretion in the stomach, salivary secretion increased. Under these circumstances, Tom and other subjects complained of anorexia, distention, gastric fullness, belching, retention of food in the stomach, "dyspepsia" and ultimately vomiting. Thus, situations which the individual found unacceptable either because of their poisonous pharmacological effect, or because they otherwise constituted a threat or assault to his security, were associated with a defensive protective reaction involving dilution, neutralization and rejection and ejection.

This is exemplified by a woman aged 24 who came to the New York Hospital complaining of fullness in the epigastrium associated with anorexia and nausea. She had been rejected by both parents, had reacted to life problems with indecision and had attempted to resolve them by rationalization rather than action. However, she did join a world movement. She felt that her own security and that of the Jews in general depended heavily upon the success of the Zionist movement. She was intubated with a gastric balloon and with another tube through which specimens of gastric juice were collected. The balloon was inflated in the stomach and connected to the kymograph. During a phase of gastric contractions of average size and frequency, her attention was called to a newly formed society dedicated to opposing the Zionist movement and exposing what they considered misrepresentations by the Zionists. She had not previously heard of the society, and she appeared disgusted and horrified to learn of its activities. She stared, pale and wide-eyed at the examiner, immobile and obviously frightened. The motor activity in her stomach promptly stopped and the organ relaxed and increased in size. Finally nausea occurred. Later discussion revealed that this individual characteristically reacted to threatening situations with anxiety in which there were strong feelings of disdain, hopelessness and despair. "When something comes up to worry me, I have a feeling of being defeated, that things are hopeless. That is how I felt when you showed me that advertisement of the anti-Zionist organization."

Akin to this, but somewhat different in their effect, were situations that were considered overwhelming and induced feelings of dejection, sadness, grief, abject prostration, despair, horror or defeat. These were associated with absent or decreased gastric motility and tone, delayed emptying and hypo- or anacidity, with pallor of the mucous membrane. Mucus and salivary secretion also diminished, and gut contractions were diminished or absent. The following account is an example of such depression of gastric function in association with fear and sadness.

Tom suddenly experienced intense fear one morning in the midst of a phase of accelerated gastric function. An irate doctor entered the room muttering imprecations about an important protocol which had been lost. The subject had mislaid it and expressed by talk his fear that he had lost the record and his job. During the ensuing minutes while the doctor was opening and closing drawers, Tom lay motionless on the table and his face became pale. Prompt and decided pallor occurred also in his gastric mucosa,

and was associated there with a fall in the rate of acid production. A minute later, the doctor found his missing protocol and left the room. Forthwith the face and gastric mucosa of the subject regained their former color.

Sadness, dejection and feelings of self-reproach were accompanied in this subject by taciturnity, lack of "energy", slowness of movement of the body generally and by pallor of the gastric mucosa, decreased acidity and gastric motor activity. Even the stomach's normal response to the ingestion of food was inhibited under these circumstances. Thus, one morning, the subject was depressed and uncommunicative over having lost, through his own negligence, an option on a house which he had long been eager to acquire. He was limp and dejected and filled with feelings of self-depreciation and refused to relate the nature of his trouble until several hours later. Beef broth was administered directly into his stoma and it was noted that the hyperemia and acceleration of acid production and motility, which regularly followed ingestion of beef broth, were partially inhibited.

A similar gastric and feeling pattern occurred when a beloved member of his family died. Other subjects were found characteristically to meet threatening or adverse life situations with feelings of defeat and dejection. These were predictably accompanied by depression of gastric activity.

It would thus appear that situations or symbols which, because of their significance to the individual, cause him to feel overwhelmed, or evoke feelings of desperation, are associated with the almost complete cessation of gastric activity. This is compatible with the view that the blow has shocked the organism and evoked an emergency pattern, in which digestive function is irrelevant and is therefore abolished.

In brief there would appear to be two varieties in the pattern of gastric hypofunction which are closely linked and which often co-exist.

1. A pattern associated with overwhelming catastrophe with feelings of fear, terror, horror, abject grief, depression and despair in which practically all gastric function comes to a standstill.

2. A pattern associated with threats or assaults that elicit feelings of disgust, contempt, or which, because of the personality and early experience of the subject, elicit patterns of ejection. In this protective reaction of defense gastric function is also reduced, but mucus production is increased as is also duodenal motor function, and the concomitant skeletal muscle contractions seen in vomiting result, again the organism behaving as though the noxious incident inadvertently ingested, could be diluted, neutralized and ejected.

*Protective Patterns of Defense: (a) Involving ventilation and the airways.* Protective reactions are also elaborated about the airways. Functional alterations in the structures of the nose have been studied and correlated with a wide variety of circumstances. These include noxious stimulation inside the nose by chemical agents, noxious stimulation of other portions of the head, variations in environmental temperature, interruption of afferent

nerve pathways, and numerous threatening life situations with their accompanying affective states.

In general, two patterns of disturbance of nasal function were recognized. The first involved vasoconstriction in the nose with shrinkage of the membranes and increase in the size of the air passages. Thus, a young man whose wife was soon to bear their first child, was terrorized when she coughed up much bright red blood. He brought her as quickly as possible to the hospital, dreading lest another hemoptysis occur, lest this symptom mean tuberculosis, long hospitalization, ruination of his life plans. Upon arrival at the hospital his nasal structures were observed to be pale, shrunken and dry. Opening of the airways allows of increased ventilation and is part of a mobilization pattern of offensive nature to be discussed below. Such changes accompanied feelings of being overwhelmed by fear or terrorized, which, however strong, involved minimal conflict.

More pertinent to this discussion of defense reaction was the second type of disturbance in the nose characterized by an initial hyperemia associated with turgescence of the erectile tissues in the turbinates and nasal septum, engorgement of the nasal mucosae and increased secretion. These phenomena occurred in reaction to local noxious stimulation on the mucous membranes and in the vicinity, and, as well, to other threats inducing significant conflict with resultant anxiety, resentment, anger, guilt and feelings of frustration. Thus, following noxious stimulation of the mucous membranes of the nose by fumes of ammonium carbonate, there was observed local hyperemia, swelling of the turbinates and increased mucus secretion. These changes were accompanied by obstruction to breathing. Also, immediately following inhalation of pollens the resultant "allergic" rhinitis in a sensitive man involved marked vasodilatation in the nose with redness of the membranes.

Noxious stimuli not directed at the respiratory passages, including painful stimulation of the head, induced similar nasal hyperemia with swelling, hypersecretion and obstruction. Special interest is attached to nasal changes which were found to be associated with conflict and with feelings of frustration and resentment and which often accompanied frank weeping or a state of being on the "verge of tears." There occurred initial redness of the mucous membranes of the nose, with extreme swelling of the turbinates and nasal mucosae, profuse secretion and obstruction. Complaints of difficulty in breathing ensued.

In general, hyperemia, swelling and hypersecretion in the nose were found to parallel one another, although after the establishment of swelling the hyperemia might subside, leaving pale, edematous, wet nasal structures. As previously observed in the skin, stomach and bladder, the turgid, hyperemic membrane of the nose was often found to have a lowered pain threshold. When threatening life situations productive of conflict were sustained, the associated nasal changes which might at first have been predominantly unilateral, became persistent and bilateral. Moreover, when swelling and ob-



struction persisted, pain and tenderness occurred and spread over the zygoma and into the temporal region. An example of such a defense reaction in the nose, and in the throat and chest as well, is as follows:

A 36-year old housewife complained of attacks of dyspnea, associated with dry cough and wheezing for the previous six months. Her parents were Russian Jews who came to America before the First World War. The father was lettered and gentle, the mother unschooled and cold; both were forceful characters. Her three sisters were married to Jewish businessmen, and the three brothers were successful as an accountant, a factory foreman and a lawyer respectively. They all enjoyed the favor of the parents, whereas the subject had incurred their disapproval by marrying a relatively non-competitive Roman Catholic of French-Italian parentage, nine years her senior.

She had been a bright, fun-loving girl who was nevertheless sensitive and wept readily. Because of precocity, she was advanced rapidly in school. She graduated from high school at the age of 16, but could not enter Normal School because she was too young. She was discouraged from becoming interested in young men by her family who told her she was too young. She was pressed to interest herself in study and shun youthful diversions. Nevertheless, at 17 she met and fell in love with a young Jewish lawyer, who resembled her father. The patient stated that he would not make love to her because he said she was "too pure and too young." In a rebellious mood she married a romantic and colorful Aryan; she looked earnestly to her husband for achievements to vindicate her defiant desertion of the family pattern. However, he obtained a job as a municipal garbage truck driver and had sharply limited aspiration. Her mother-in-law interfered in the conduct of her household, saying she was "too young" to manage her affairs. The patient ate excessively and became obese. Her daughter was born after three years of marriage, her son six years later.

She was ambitious to improve the social status of her children by educating them. Her daughter, at the age of eight, developed diabetes mellitus, which increased the patient's insecurity and further threatened her ambitions. At this time she was becoming increasingly disappointed, anxious and resentful, and had difficulty in breathing through her nose. This nasal obstruction developed suddenly when several women in her presence condemned a girl for "overstepping conventions." It continued, and grew more and more troublesome, and a year later she had nasal polyps removed.

After another 12 months (November, 1945) her son became ill with abdominal complaints and the subject feared that he, too, might have diabetes. At this time she developed attacks of wheezing during the night. These increased in frequency until she soon was having persistent respiratory distress with an accompanying dry cough.

She came for study during a symptomless period, practically free of wheezing. Her nasal mucous membranes were examined and found to be moderately pale (40 on the color scale). The turbinates were flat (1 + swollen) and the airways open. For several minutes a discussion ensued of her daughter's diabetes, and of why she had married her husband. Another examination of her nose was made. The subject began to wheeze. Her nasal mucosa was now redder (60 on the color scale) but the turbinates showed no more swelling and there was, as yet, no obstruction nor increase in secretion. During the intravenous injection of 0.25 gram sodium amytal, she became relaxed, smiled, and her wheezing disappeared. She was then asked questions about her former fiancé, and she talked about having thrown away opportunities for marital happiness, economic security, productive offspring and favor with her family. She complained that she had lost her figure and had become obese and had relatively little to look to in the future. Wheezing and coughing became severe.

At this point her nasal mucous membranes were bright red (70-80 on the color scale), wet, turgid, swollen (3+) with hyper-secretion and there was almost complete obstruction to breathing through both nares.

She was again interviewed during a period of mild status asthmaticus. In the hypnoidal state induced by 0.5 gram sodium amytal, five minutes following the intravenous injection she was lying comfortably without respiratory distress or wheezing, nor were abnormal sounds heard when her chest was auscultated. A conversation was started. When she spoke of her father she began to wheeze and complain that she could no longer breathe comfortably through her nose. She said he was kind, but that he "pushed" her ahead in school and would let her have no "pleasures." She talked about her husband's inadequacies in learning and earning, and of her disappointment in her children. "I hoped they wouldn't be wild like they are and would grow up to be nice people." Her wheezing was so severe that she had to sit up and had difficulty in talking. Her nose was completely obstructed. At this point she was urged to elaborate a fantasy about going to a dance with a group of gay friends, and a second time the wheezing stopped for five minutes. But, when the suitor, who had thought her "too young," was discussed, she became tense and sober and the wheezing was again almost as marked as it had been before. Once more the patient was diverted by jovial remarks. She relaxed and was free of wheezing and nasal obstruction, 45 minutes after the beginning of the observation.

In short, when faced with assault or threat, the activities of this woman were such as to involve herself more deeply in her difficulties rather than to free herself by taking action. Her general behavior through the years had, so to speak, been one of "cutting off her nose to spite her face."

Against local intrusion, this protective response, which is characterized by shutting out the noxious agents and neutralizing their effects by dilution and washing away, may prove highly effective. But, against situational threats involving interpersonal relations, the nasal and other airway changes in this patient afforded incomplete relief and were often productive of discomfort.

Such morbid developments seemed to be relevant to illness in a large proportion of a series of patients carefully studied who had chronic or recurrent nasal disease and "sinusitis." For example, in one individual observed daily during eight months, nasal hyperfunction which accompanied a period of serious frustration and conflict resulted in pain under the zygoma and headache together with hyperalgesia and redness, clinical features often noted with sinusitis." Antral empyema was not demonstrated, although even slight stimulation of the engorged and extremely sensitive nasal structures reproduced or intensified the pain.

Also, the diaphragm may participate in such a defense reaction. For example, in certain persons during periods of threat the dome may flatten and the excursion diminish due to sustained contraction of the muscular sheet. The patient then complains of difficulties in getting "a full breath," and tight "cramp" sensations in the substernal region. The muscles about the chest and neck may also exhibit sustained contraction, thus further increasing the difficulty in ventilatory exchange.

There appears to be some broad biological significance to this reaction of

shutting out and washing away at the head end of the organism. During weeping, the nose, as well as the eyes, participates in this reaction; furthermore, in some individuals, deeper structures including the bronchi and the diaphragm constrict during threatening situations, thus participating in the reaction of exclusion.

Respiration consists of an in-and-out circulation of air through the respiratory passages. Shutting out thus involves equally a shutting in. In effect, the organism diminishes its exchange with its environment. An individual limits the extent of his participation in the situation about him. Thus insulated, he takes in less and gives out less. "Shutting out" then becomes part of an overall reaction of non-participation and its "shutting in" aspect may include the repression of resentments and conflicts.

The "shutting out-shutting in" pattern, especially when maintained for long periods, is evident in the personality features and social behavior. As in all individuals expressing conflict between divergent purposes, the character develops distinct facets, some expressing drives which are unacceptable in terms of the individual's standards. The subject may be unaware or incompletely aware of his conflicting aims.

As a result of the conflict of forces in this unstable equilibrium the overt behavior of the subject may be that of quiet bravery and hard work, or of "smiling through tears," progressing to frank whimpering and clinging, or any combination or alternation of the conflicting elements. The content of the behavior appears to be: "Everything is 'just fine,' but look at my plight! Lend me support. Is it right that I be exposed to such trouble? 'Can't something be done about it? It isn't my fault. Don't you, too, abandon me."

Subjects exhibiting the "shutting out-shutting in" pattern are essentially defensive and "close mouthed," talk with difficulty about relevant personal matters and seldom take steps to improve their state. Yet aggression may be evident in the pursuit of a beloved object or desperate clinging to that which lends security. A lively show of love and affection is a basic requirement and is readily accepted. In many who are deprived of devotion and tenderness in early life, events which threaten such emotional support in later life induce exacerbations of the defensive reaction.

If the individual's insecurity mounts, and threats, therefore, become more hazardous, ultimately the dual program may no longer be maintained. The patient then presents a picture of sad and petulant protest, crying for help and struggling for breath.

*Protective Patterns of Defense: (b) Involving the esophagus as well as the bronchi.* Faulkner has reported other examples of the "shutting out or non-participation reaction" in the esophagus and bronchi of subjects during examination with an esophagoscope or a bronchoscope. Thus a man, aged 75, complained of being unable to swallow solid food and of having difficulty at times in swallowing liquids. These dysphagic symptoms had developed

suddenly three weeks previously when he had been informed that he was to be denied continuance of his \$40.00 a month "old age pension" from the State. Relief authorities had discovered that he had savings in excess of the amount which entitled him to State assistance.

Faulkner observed in this man contraction of the entire length of the esophagus. When the patient was asked to imagine how it would feel to be put back on the pension roll again, the walls of the esophagus relaxed and the lumen opened. Faulkner then bronchoscoped his patient to ascertain whether or not similar narrowing would be found involving the tracheo-bronchial tree, and if so, whether this would also respond to suggested threats, or assurance. He observed that the lumen of the right main bronchus was reduced in size to one-third its usual diameter. There was definite limitation of movement of the walls of both the bronchus and the carina or bifurcation. The customary luminal widening on inspiration and narrowing on expiration were absent. When asked to recall how he felt when the candidate he favored won the recent Congressional election, the lumen of the bronchus immediately widened appreciably and showed the usual inspiratory widening and expiratory narrowing.

Discussion had revealed that his Congressman's victory was associated with the hope that his pension would be continued. When asked how he would have felt had his Congressman lost, the bronchial lumen immediately narrowed again until it was one-third of its original size. Furthermore, when asked how he would feel if he were to be promptly restored to the old age pension list and assured that he would positively remain on it for the balance of his life without further investigation, the bronchus opened widely, breathing became deep and normal and inspiratory and expiratory bronchial movement began again. But at the suggestion that he might never again receive his pension, and at his age be forced to find employment when so many were already unemployed, the lumen again narrowed, the bronchial walls quivered and breathing became short, labored and rapid. Faulkner subsequently confirmed these findings on a series of patients.

It therefore appears from these observations that the respiratory, alimentary, orbital and other skeletal muscle patterns of the head and elaborate verbal, interpersonal and social patterns may act as a unit of function or separately in shutting out an environment that is literally or symbolically noxious.

*Protective Patterns of Offense: (a) Involving cardiovascular and ventilatory functions.* Such shutting-out, non-participation patterns stand in contrast to those described by Cannon, who observed short-lived changes in the hostile cat confronting the barking dog. Under these circumstances, there occurs a diminution of salivary secretion, and circulation. Digestive activities stop and food may remain for hours in the digestive canal without being acted upon. The heart beats faster, the blood pressure is increased and there is redistribution of blood in the body with less in the organs of

digestion and more in the muscles. The cat is in an optimal state for fight or flight, ready to be the attacker or the attacked, the pursuer or the pursued. The struggle which follows may determine life or death. Under these circumstances the great muscles of the limbs and trunk may be used in strenuous and prolonged effort. Digestion is of secondary importance if life is at stake. In addition, great effort is associated with a large increase in the amount of air that is breathed into the lungs and out again, and the widening of the bronchioles and shrinkage of the nasal structures facilitate the total movements of air.

Thus, all these apparently disconnected changes, including those in the respiratory passages, become a part of a single process. They are directed towards making the total organism more effective in the struggle. It is clear, moreover, that in such an urgency the element of inner conflict is minimal.

However, in man, the mobilization pattern may be as readily associated with conflict as other bodily patterns. Indeed, among subjects with essential hypertension, strong conflict with repression of hostility has been recognized as a characteristic feature. It is evident that the biologic pattern is one for action. The following instances illustrate such an action pattern in relation to symptoms.

A 50-year old Jewish male "cloak and suit" worker had had hypertension from time to time during 10 years. He complained of lightheadedness on exertion and headache, substernal pressure and painful precordial sensations not related to exercise. His symptoms followed a recent upper respiratory infection. The examination, on hospital admission, revealed a blood pressure of 210 mm. Hg systolic and 120 mm. diastolic, and a slightly enlarged heart. His electrocardiogram showed depression of  $ST_{1 \text{ and } 2}$ , low amplitude of  $T_{1 \text{ and } 2}$  and slight left axis deviation. The patient was interviewed while on the ballistocardiograph bed, and respiratory, pulse, blood pressure, and cardiac output measurements made. The resting level of blood pressure was 175 mm. Hg systolic and 100 mm. diastolic. The interview revealed that the subject had an uncompromising, demanding wife who imposed her relatives upon the patient in his business; she "cared" little about his personal well being. She complained when the patient felt obliged to visit his aged mother; but when the patient acquiesced to her demands and remained at home, she went out to visit her friends and left the patient alone. During this narration, the subject at first sobbed and then became angry and poured out instances of his wife's iniquities. He complained that the "aggravation" aroused by the discussion was characteristic of what he experienced much of the time, especially when at work or at home. Specifically he noted choking sensations, substernal pressure without radiation and occasional giddiness. The blood pressure was elevated from 175/100 to 220/130 and cardiac output rose 40 per cent during the interview. The patient complained of precordial sensations. The cardiogram changed slightly but definitely with elevation of the ST segments and of the T waves (which Master considers a positive test for coronary insufficiency). The functions did not return to resting levels at the end of the interview and reassurance was not effectively produced. Respiratory tracings showed shallow rapid respirations identical before and after the interview. The same electrocardiographic changes and symptoms subsequently were produced by the effort involved in the Two Step test.

A second example of a reaction pattern involving cardiovascular and respiratory function is as follows:

A 34-year old woman complained of attacks of nocturnal dyspnea. She had essential hypertension with no evidence of irreversible vascular disease. She was interviewed while lying on the ballistocardiograph bed. Records of respiration, pulse, blood pressure, and cardiac output were taken before, at intervals during and after the interview. She was told to talk freely and not hesitate to display her feelings. Her statements were recorded and chronologically related to the physiological observations. The interview itself represented a stress-producing situation. During the interview the patient was aware of and complained of feelings of isolation and loneliness because of her husband's absence. (He was in the Army and overseas.) She described working for a perfectionistic employer under work conditions which all recognized as difficult and which made "perfect work" impossible. Nevertheless, her employer, during his tension states, loudly disapproved of the patient's performance; and the latter, herself a perfectionist, was deeply hurt and enraged. During her married life and before her husband's departure she was able at the end of the working day to voice her anger and regain her personal dignity through her husband's sympathy and support. But after his departure and because of her stand-off, aloof manner, which precluded confidential discussion with friends, her suppressed anger turned to rage and her tension mounted. At the time of the interview she was aware only of tension, but told about obsessive and morbid fears. The fear of poisoning from the gas jet of her refrigerator caused her to turn it off at night. More lately she had feared that she might hurt someone or herself. She also had murderous dreams.

During the interview with this patient, the blood pressure was elevated from 125/90 to 185/120 and the cardiac output was elevated 20 per cent over the resting level. They returned to resting levels after reassurance and a hopeful formulation. Respiratory tracings done before and after the interview demonstrated that as a result of the interview the minute ventilation doubled and the utilization coefficient halved, without significant alteration in the oxygen consumption.

The effects in this patient on blood pressure, cardiac output and respiration were as great or greater and more prolonged during recall of disturbing life situations than following exercise, which was tolerated well. The patient complained of awakening at night with a sensation of constriction in the throat, palpitation and shortness of breath. These symptoms stemmed from an increased stroke volume and increased respiratory ventilation. The patient did not have paroxysmal nocturnal dyspnea associated with failure of the myocardium, but she nonetheless was shown to have under circumstances of stress increased minute ventilation, increased stroke volume and increased cardiac output. After three days in the hospital not "on bed rest" her blood pressure fell from 180/120 to 130/90. The removal of the patient from her threatening environment was probably a major factor in this change. The ventilatory response to the assaults of her situation was the cause of dyspnea in this patient. The dyspnea was a matter of over-ventilation rather than being related to increased need for oxygen.

*Protective Patterns of Offense: (b) Involving the pressor reaction and renal vascular function.* It would appear that many of those who in early life exhibit transient though significant pressor reactions to assault or threat gradually raised the basic level of their systemic arterial blood pressure. Thus a significant proportion of men who exhibited a transient rise in blood pressure from average levels during an initial army physical examination, subsequently developed sustained hypertension. It is obvious that many variables operate in determining whether any inborn protective pattern will assume clinical importance. But it is conceivable that the sustained state of threat in which certain of these persons lived caused inconsequential events to assume special importance, resulting in their remaining in a state of almost continuous readiness for action. The mechanisms implicated in an essential hypertension are unknown, but in one way or another, the kidney is usually involved and therefore consideration of renal blood flow becomes of interest.

It has been demonstrated that renal hemodynamics and excretory functions are relatively stable in any one individual under basal conditions, but may be modified by various chemical agents and procedures. Indeed, profound modifications of renal blood flow were noted by Homer Smith during two disturbing incidents in persons with average levels of blood pressure; in one, a rumor concerning his possible unanticipated and unwanted discharge from the hospital reached the subject; and in the other, a misunderstanding arose concerning the significance of the clearance procedure. Both subjects seemed frightened. The effects were as great as those of a moderate amount of epinephrine. Together with a rise of blood pressure, there was a considerable decrease in effective renal plasma flow and a lesser change in glomerular filtration rate. In our laboratory it was demonstrated in persons with average blood pressure, that similar changes in renal blood flow accompanied both noxious stimulation of the head, and pain induced by cold.

The pathogenesis of the disturbance in essential hypertension is still undetermined. One group of workers showed that in animals, interference with renal blood flow under certain conditions results in chronic hypertension that has many of the features of essential hypertension in humans, but whose precise relationship to human hypertension has not yet been clarified. Another group has done experiments in dogs which indicate that vasoconstriction within the kidney induced by faradic stimulation of renal arteries results in significant reduction in renal function together with rise in systemic arterial blood pressure.

That changes in renal blood flow may be pertinent to the subject with essential hypertension is indicated by the fact that the blood flow in his kidney is small in terms of functioning kidney tubular mass, that is to say, the hypertensive kidney is relatively ischemic as compared to the normal. Also, the degree of depression of renal blood flow parallels approximately the duration and severity of the hypertension. The order in which events

proceed is indicated by the fact that the glomerular filtration rate in early hypertension is entirely within normal limits, but with advanced hypertension and reduction in the number of functioning glomeruli, the glomerular filtration rate is also gradually depressed. In all instances the ratio of renal blood flow to tubular mass is low, indicating a relative ischemia of the hypertensive kidney. As the hypertension advances, the tubular mass decreases but always in such a manner that the renal blood flow is poor in terms of the existing tubular mass. These facts suggest that a defective renal blood flow precedes the onset of faulty excretory function. If kidney ischemia be at all relevant to the occurrence of arterial hypertension, renal blood flow studies in those with widespread vascular reaction to threats become of interest. But before pursuing this topic further, pertinent aspects of the personality of such subjects should be appraised.

Thirty-five subjects with essential hypertension, selected on the basis of their willingness to coöperate, were studied. In essence, insofar as these patients were concerned, the subject with essential hypertension presents a personality which is the resultant of divergent drives. His appearance, movements, manner of speech and interpersonal behavior bespeak one who, when confronted by a threat, or by a dilemma, takes action. He is a tense man, poised and "calm," one who has all the reins in his fingers, but who finds that the task requires constant alertness and readiness to spring into offense.

However, he is prevented from acting offensively and he appears gentle, generous, outgoing, sweet mannered and with much and hearty laughter. When, through repeated threats, the underlying hostility is barely repressed and near the surface, sternness, austerity, ineffectiveness, thinking difficulties, irascibility and grim determination, sometimes featured by mirthless laughter, dominate. Then the state of the individual becomes so precarious that threats or noxious stimuli which would be considered relatively minor, such as plunging the hand into cold water, call forth a major pressor response. At such times the patient may present easily recognized features of his anxiety. During "Amytal" hypnoidal states, he may describe feeling as though "something is hanging over my head." Ultimately he may become tense, agitated or depressed.

In view of these facets of the character and personality, it became of interest to investigate renal hemodynamics in subjects with essential hypertension during rise in blood pressure initiated by threats in the form of discussion of topics known to have a significant relationship to the personality structure.

Situations or threats that jeopardized the security based on the subject's need of approval or love from members of the family, or from authority, were, to those studied by us, especially disturbing. Exceedingly important in several men was the fear of being disapproved by the mother. Indeed, symbols that aroused this basic conflict produced visible evidence of tension, with accompanying pressor reactions of considerable magnitude.



In 18 of these hypertensives without evidence of renal disease, or abnormality of renal function by the usual clinical tests, renal blood flow and glomerular filtration rate were ascertained by the now well known para-amino-hippuric acid method. The first procedure carried out after the arrival of the patient was catheterization with a No. 16 Foley soft rubber catheter in order to permit him to become used to the sensation and allow about an hour and a half for him to reach a basal state. Sodium para-amino-hippuric acid was used for the estimation of effective renal plasma flow and inulin for glomerular filtration rate. Clearance for successive periods of 15 and 20 minutes were measured over about two hours. The first two or three clearance periods were utilized for controls during which the patient was reassured and every effort made to prevent sensitive topics from being brought up. Then, during the next one or two periods of 20 or 15 minutes each, topics of known importance were abruptly introduced, usually having to do with interpersonal relations between the patient and members of the family. Following this, the discussion was turned to neutral topics and an attempt made to engender feelings of security in the patient, during which time several additional clearances were determined. Blood pressures were measured at frequent intervals. At various points during the procedure some of the patients received sodium amytal. The following protocol is representative.

A 41-year old married Jewess had been found to have an elevated blood pressure a year and a half ago. She complained of a frequent dull ache on top of her head and a sensation "like a tight hat" around her head. Outwardly she presented a show of "calm" and a bland attitude and claimed she led a "really happy life." But doing her housework, she said, "got her excited" and left her feeling exhausted.

In the hospital, she was observed during an interview, and her blood pressures recorded at intervals. At first she appeared tense, and was anxious concerning the procedure of the interview (B.P. 188/104, dropping to 148/88 while talking of pleasant, neutral topics). When abruptly asked, "How are things at home?" blood pressure rose to 180/88. She indicated strong dependent needs for love and praise from her husband and described him as considerate and thoughtful (B.P. 198/108). She told of her greatest emotional crisis occurring when she received a telegram which she was reluctant to open lest it tell of her husband's death. "I screamed and yelled" (B.P. 196/100). "I felt considerable relief when I found it contained news of the death of my mother" (who had given her little affection and whom she hated). She became tearful in expressing resentment against her mother "for the way she treated my father" (B.P. 196/100). Again, when she spoke of her father as being "gentle and kind," her blood pressure was 186/106.

During the interview and pressor response, the renal blood flow decreased approximately 25 per cent and peripheral resistance in the kidney increased 40 per cent. The patient was then urged to relax, and was given an intravenous injection of 0.25 mg. of sodium amytal. Blood pressure fell rapidly to 140/88 and remained there for the next 15 minutes, though renal blood flow continued to remain at a lower level than before the injection of Amytal.

Later she was interviewed during an hypnoidal state following intravenous administration of 0.3 gm. Sodium Amytal. Before the injection, blood pressure was 255/125. In the hypnoidal state she became well relaxed and began to talk freely.

Blood pressure fell to 170/110. When she told of receiving the telegram she mentioned above, blood pressure became 195/130. There was a fall to 180/120 when she spoke of taking life realistically. She next mentioned her hatred for her mother and discussed her father's death. Blood pressure rose to 230/150. When she began to joke with the physicians there was a precipitous fall to 170/120.

This woman, with essential hypertension, presented a reaction to threats featured by hostility and resentment, and an attempt to deal with threats by action. However, there was an associated prominent need to placate, to maintain peace at any price. Therefore hostility was repressed and action directed elsewhere than at the real danger. This misdirection led to incomplete resolution of the problem and further frustration.

Rises in diastolic and systolic blood pressure were similarly induced in 17 other persons with essential hypertension by discussion of topics of personal significance, usually having to do with family interpersonal relations, without, at the same time, inducing outward evidence of strong emotional reaction. The rise in blood pressure under such circumstances was accompanied by renal vasoconstriction which was either proportional to that of the body as a whole or more intense than necessary to compensate for the rise, reflected by decreases in renal plasma flow of 17 per cent to 25 per cent of control level. In some patients renal vasoconstriction outlasted the rise in systemic blood pressure. This became conspicuous when the degree of peripheral resistance in the kidney vascular apparatus was appraised, and represented an increase in resistance of as much as 40 per cent. The increase of renal vasoconstriction was located principally in efferent glomerular arterioles although both efferent and afferent arteriolar constriction occurred. Fall in blood pressure during induced feelings of security was accompanied by vasodilation of the efferent and afferent arterioles.

From these and other facts, it may be inferred that the kidney in persons with arterial hypertension exhibits an abnormal vascular pattern, characterized by increased arteriolar tone, and the latter may be further increased by threats or assaults that evoke protective reactions of a pressor nature.

However, it may not be inferred that the experimentally induced renal vasoconstriction is the cause of the observed hypertension. Thus, preliminary observations have revealed that patients with arterial hypertension exhibit a pressor response during experimentally induced stress both before and after thoracolumbar sympathectomy (T7-L3), although the renal vasoconstriction elicited before is no longer demonstrable after sympathectomy. It is apparent from these observations that the blood pressure may still rise in response to threats, even though the kidney does not participate in the vascular reaction. Secondly, it was possible to demonstrate in those with and without arterial hypertension that the renal blood flow is not increased as the result of renal denervation by sympathectomy, but remains unchanged or may actually be decreased. In one non-hypertensive subject with a unilateral kidney denervation (sympathectomy) equal blood flow in both organs was observed. The meaning of these observations on the relation of

adrenergic impulses and kidney blood flow to arterial hypertension in well established hypertensives is not clear. Certainly, as far as can be demonstrated in the latter, renal vasoconstriction due to sympathetic impulses is not the essential defect in the mechanism of hypertension. Nonetheless, there remains the probability that neurogenic factors are pertinent to the beginnings of the hypertensive syndrome. It is suggested that as part of the protective reaction early in the life of the potential hypertensive, adrenergic impulses induce neurohumoral effects involving the adrenal cortex and the kidney which ultimately result in irreversible kidney ischemia and arterial hypertension.

Furthermore it is suggested that such renal vasoconstriction may, if prolonged, damage the renal blood vessels and the parenchyma, and lead secondarily to further elevation of blood pressure. The cost of the reaction to the heart and to the vascular apparatus of such organs as the brain and kidney may ultimately be great enough to destroy the organism.

*Inappropriate Use of Protective Patterns.* Nasal obstruction, though effective in keeping out dust and irritant gases, is less effective against blows or unrequited love. As mentioned above, closing the air passages and increasing the mucous membrane secretions minimize the damaging effects of a gas or of an irritant particle, but such devices do not protect against a thorn in the foot or make less destructive the hostility of a parent or marital partner. Indeed, they often lead to additional distress. The closure of the esophagus protects the stomach from a corrosive agent but does not protect the child from neglect by its parents or resolve the resentment of a rejected husband. In short, the shutting-out and washing-away pattern is another of those ancient protective devices which have specifically beneficial effects under certain and limited circumstances. It fails under others just as the total reaction pattern described by Cannon fails to serve the stockbroker watching a ticker tape that may spell disaster. Thus, the human organism in reaction to threats uses devices which may be inappropriate, but the setting in motion of an integrated pattern of reaction devised to deal with threats appears to afford a measure of relief from anxiety and tension.

*Mixing of Protective Patterns.* The various biologic patterns involved in protective response to assaults or threats fall, as mentioned above, into offensive and defensive categories. A single individual usually operates in one or another frame, but he is likely from time to time to vary his methods, alternately using defensive and offensive patterns and occasionally sustaining both types of effort simultaneously. Such behavior may reflect the state of conflict of the individual as to how to deal with a threat, whether to take action against it or exclude it. The patterns may appear divergent, but are not in opposition in the broadest sense, both being aimed at protection of the organism.

It is in this light that the coexistence, for example, of gastric hyperfunctioning (with or without lesions) and nasal obstruction can be viewed. The nasal obstruction implies an attempt on the part of the organism to shut

out, rather than to deal with the situation. Gastric hyperfunctioning, on the other hand, implies readiness for action.

The result of conducting two campaigns at the same time is a costly expenditure of energy. This duality of method is further illustrated in the trembling, fidgeting and tapping of the feet, coupled with sustained muscular contraction which probably represent the incomplete resolution of a drive to move away from the site of the dangerous situation, opposed by a stronger drive compelling the individual to remain in place to face whatever befalls him. It would appear that once a bodily pattern of reaction to some threat has been set in motion, however inadequate may be its protection, the anxiety and other uneasy feelings which accompanied it initially may become secondary, thus to remain for indefinite periods.

Some of the reactions to threats are accompanied by bodily changes that are called to the attention and may be the basis for complaint (nose, stomach); of other reactions the individual may not be aware until long after the pattern has been established, and irreversible tissue damage has resulted.

*Stock Factors, Organ Selection and Inferiority.* Dominant protective reaction patterns are apparently deeply ingrained since they occur in many individuals of the same stock under analogous conditions. It seems likely that they are stockbound, analogous to the retriever pattern in dogs, running pattern in the horse, hoarding in squirrels, building and space orientation in birds and insects, and sham death in the opossum. The implication is that the individual and his clan meet life in a particular way, and to a degree, in a different way from the members of other stocks. A given protective pattern may during long periods of relative security remain inconspicuous, and then, during stress, become evident as a disorder involving respectively the gut, the heart and vascular systems, the naso-respiratory apparatus, the skin and general metabolism.

When one asks why one organ rather than another is involved during stress, there is no satisfactory answer. More profitable is the question of how the organ is implicated in a biologic pattern of offense or defense.

The repeated or prolonged participation of a given organ in a protective pattern is not evidence of the weakness or inferiority of that organ even though because of such participation it fails to maintain its structural integrity. True, involvement of the part may indicate that the individual is weak or living under undue stress, but the organ can hardly be said to be weak, and indeed may be especially developed and strong.

*Destructive Results of Protective Patterns.* For the most part, protective devices are designed for short term use and as such fall well within the physiologic budget of the organism. Thus, transitory changes in nasal function indicative of being on guard, like the transitory elevations of blood pressure and gastric function which may similarly follow threats, are well tolerated. The difficulty arises when the threatened individual sustains emergency patterns as "the way of life." The time necessary for the occur-

rence of structural changes in some tissues may be hours, whereas in other instances long periods would seem to be required. Furthermore, the protective pattern once established often creates fresh disturbances in and about the organism, increasing its vulnerability so that new threats perpetuate the need for protection; therefore, disturbances may persist long after the initial threat ceases to apply. For example, compulsive individuals who need to "outdo" others find that their behavior creates new foes, which requires perpetuation of the protective pattern. Also, it has been shown elsewhere that during gastric hyperfunction, as a part of the protective pattern, when highly acid gastric juice comes in contact with an unprotected eroded surface, a vicious cycle is created in which further stimulation to hyperfunction occurs.

Again, as elsewhere in the body's ducts and cavities, the establishment of obstruction within the nasal cavities often leads to secondary infection. Minor anatomical deformities such as spurs or deviations of the nasal septum may assume significance when the already narrowed airways become occluded by swelling of the turbinates consequent upon some threatening life situation. Once it has taken root an infective process can prolong the period of morbid changes in the nose and lead to serious disease and incapacity long after the precipitating emotional conflict has been resolved.

Serious incapacity on the part of the patient may also occur when only minor structural changes are present. As noted in earlier studies on headache, many patients over-react to minor disturbances or sensations when that site takes on special meaning with regard to the integrity of the individual. For instance, past conditioning experiences may endow the nose with special significance and cause minor disturbances in nasal function to have ominous implications for the individual.

As the processes of defense and offense may lead to disastrous results in the airways, stomach, heart, blood vessels and kidneys, so may the repression of emotions associated with these patterns prove destructive to the whole individual.

The formulation here presented illuminates certain well defined reaction patterns. It is evident, however, that some reaction patterns accompanying life experiences are not clarified by this concept. For instance, there are widespread bodily changes and symptoms that occur in some individuals during the period immediately following stress or emergency. Thus headache, vasomotor changes, vomiting, diarrhea and other gastrointestinal dysfunction, changes in amount of tissue fluids, dejection, fatigue, prostration may be absent during the period of duress, only to occur shortly after. Also, there are bodily changes which seem to represent the purposive or quasi-purposive attempts at some immediate or obvious gain, as exemplified by the man who develops a reversible palsy in one arm when called upon to enter battle. Although such adjustments may conceivably be protective in nature, or sequelae of protective reactions, it may be more profitable to see them as implying the existence of other, as yet ill-defined, adaptive mechanisms.

## EPITOME

Interference with or threat to his life or love, or blocking the proper fulfillment of an individual's potential, causes him to react as though to assault. He responds defensively or offensively, or both, depending on his nature, his past experience, and the situation. Under these circumstances he struggles to regain what has been lost and to rid himself of interference, in order to fulfill his drives. Such struggles evoke what may be called emergency or crisis protective patterns.

A considerable part of the human equipment has to do with meeting emergencies and dealing with crises. Protective reactions are set off by threats usually in the form of symbols, which have been connected with danger in the past.

Some of these reactions represent widespread mobilizations to provide extra fuel and energy for vital parts of the organism. Others appear to be focused on regional defenses, notably at portals of entry and exit. Offensive and defensive, general and local protective devices may operate together and separately.

Along with these conspicuous bodily preparations go certain feelings and attitudes which, stemming from the same needs, have the same goals.

The organism sacrifices at such times some functions or capacities for the sake of promoting others that are most important to meet the adverse situation. Although there is a degree of specialization in the sense that one or another protective arrangement is dominant, discrimination is not exact. In a threatened man it is common to find a variety of protective reactions, some of which are extremely pertinent, others less so, and still others minimally effective.

Because his drives are primitive and even violent, they may be out of keeping with a man's conception of himself and therefore unacceptable. Thus, the drive denied or not fully recognized by the subject, the subsequently evoked protective reaction patterns may unwittingly become sustained. A few of these reaction patterns have been intensively studied.

During assaults or threats arousing conflict with anger and a pattern of offense, the stomach prepares itself for eating with increased blood flow, acid secretion and motility. The gastric mucosa may become turgescient and the blood vessels friable. With forceful gastric contractions, bleeding readily ensues and erosions of the mucous membrane may follow.

Conspicuous among defensive protective reactions are those involving the nose and airways. It has been observed that in reaction to assault, certain individuals occlude their air passages and limit the ventilatory exchange by vasodilatation, turgescence, hypersecretion and smooth and skeletal muscle contractions. The changes, especially in the upper respiratory airways, give rise to a variety of symptoms, notably pain and obstruction, the latter often leading to secondary infection, and the prolongation of morbid processes.

Also, a non-participation behavior pattern and attitude is exhibited in inter-personal relations.

Offensive protective reactions involving chiefly the cardiovascular and renal systems were exhibited in certain aggressive individuals. These persons, in reaction to assault, mobilized their equipment, causing the work of the heart to be greatly increased through increased rate, output and peripheral resistance. Especially notable in those with pressor reactions and essential hypertension was a significant reduction in renal blood flow during periods of experimentally induced assault, an effect with potentially ominous implications.

It is suggested that when the individual maintains such emergency measures, symptoms and tissue damage may follow.

In brief, man, feeling threatened, may use for long-term purposes, devices designed for short-term needs. Costly protective activities are essential and life saving. They are devised for fleeting emergencies so that he may destroy those forces that threaten his survival. But, they are not designed to be used as life long patterns, and when so utilized, may damage structures they were devised to protect.

These considerations constitute the basis of a good deal of human suffering and sickness. To prevent these disorders, more knowledge concerning the origin of these patterns in childhood is necessary. To interrupt them once they have become well established requires a vigorous and fresh approach to methods and means. To deal with these disturbances, it is necessary to study the functions of organs widely separated in the body, and because the methods require cutting across the lines which usually separate the various medical skills, the horizon of the physician must be broadened. It follows that interest in these illnesses cannot be limited by delineations of a new specialty. The pursuit of these matters is a prime medical responsibility of our day.

#### BIBLIOGRAPHY

- ALMY, T. P., KERN, FRED, and BERLE, BEATRICE B.: Alteration of the function of the colon in man under stress. Presented June, 1947, to the National Gastrointestinal Society, Atlantic City.
- CANNON, W. B.: Bodily changes in pain, hunger, fear and rage, 1929, D. Appleton and Company, New York.
- DARWIN, CHARLES: Expression of the emotions in man and animals, 1872, John Murray, London.
- FAULKNER, W. B.: Influence of suggestion on size of the bronchial lumen; bronchoscopic study and report of one case, *Northwest. Med.*, 1941, xl, 367.
- GOLDBLATT, HARRY: Renal origin of hypertension, *Physiol. Rev.*, 1947, xxvii, 1.
- HART, BERNARD: Psychopathology, 1927, The MacMillan Company, New York.
- HOLMES, THOMAS H., GOODELL, HELEN, WOLF, STEWART, and WOLFF, H. G.: The nose, Charles C. Thomas, Springfield, Illinois, in press.
- KOTTKE, F. J., KUBICEK, W. G., and VISSCHER, M. D.: Production of arterial hypertension by chronic renal artery nerve stimulation, *Am. Jr. Physiol.*, 1945, cxlv, 38.
- LEVY, R. L., WHITE, P. D., STROUD, W. D., and HILLMAN, C. C.: Sustained hypertension, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 77.

- MITTLEMANN, BELA, and WOLFF, H. G.: Emotions and gastroduodenal function. Experimental studies on patients with gastritis, duodenitis and peptic ulcer, *Psychosom. Med.*, 1942, iv, 5.
- PAVLOV, I. P.: Conditioned reflexes, 1927, Oxford University Press, London.
- PFEIFFER, J. B., RIPLEY, H. S., WOLF, S., and WOLFF, H. G.: Experimental observations on the occurrence of arterial hypertension as a reaction of the human organism to situational threats: correlation with changes in renal blood flow, *Trans. Assoc. Am. Phys.*, 1947, ix, in press.
- SELYE, HANS: General adaptation syndrome and diseases of adaptation, *Jr. Clin. Endocrin.*, 1946, vi, 117.
- SHERRINGTON, SIR CHARLES: The integrative action of the nervous system (1906, Charles Scribner's Sons, New York), 1947, Cambridge University Press, Cambridge, England.
- WOLF, G. A., JR., and WOLFF, H. G.: Studies on the nature of certain symptoms associated with cardiovascular disorders, *Psychosom. Med.*, 1946, viii, 293.
- WOLF, S., and WOLFF, H. G.: Human gastric function. An experimental study of a man and his stomach (Second Edition), 1947, Oxford University Press, New York.
- WOLF, S.: Diaphragmatic spasm. The mechanism of a common variety of dyspnea, *Jr. Clin. Invest.*, in press.



# EFFECT OF THE ANTIMONY COMPOUNDS, FUADIN AND TARTAR EMETIC, ON THE ELECTROCARDIOGRAM OF MAN; A STUDY OF THE CHANGES ENCOUNTERED IN 141 PATIENTS TREATED FOR SCHISTOSOMIASIS \*

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## INTRODUCTION

DURING 1945 there were admitted to Harmon General Hospital 488 patients with proved or suspected *Schistosomiasis japonica* acquired during the campaign on Leyte in the Philippines. These patients have been the subject of an intensive and detailed study.<sup>1</sup>

Because the drugs tartar emetic (antimony potassium tartrate) and fuadin (antimony pyrocatechin disulfonate of sodium) used in the treatment of this disease have been reported to cause serious cardiovascular reactions and even death,<sup>2</sup> frequent electrocardiograms were taken during treatment to determine what changes might be expected. In a significant number of patients the changes in the electrocardiogram were striking and might have been mistaken for evidence of myocardial damage. In no instance did the clinical behavior of the patient warrant such a diagnosis. The changes induced, their reversible nature and significance form the basis of this report. For the guidance of medical officers a preliminary note on the changes observed in the first 66 patients treated has been published.<sup>3</sup>

## LITERATURE

Although tartar emetic and fuadin have been used extensively in the treatment of schistosomiasis in endemic areas, there exists a paucity of references to the effects upon the electrocardiogram of man. In Egypt alone, Khalil<sup>4</sup> in 1936 estimated 1,000,000 courses of antimony treatment a year were given with a mortality of 0.2 per cent. A complete review of the literature up to 1938<sup>5</sup> contains no reference to the electrocardiographic changes induced by antimony compounds.

In cats changes have been described in the electrocardiogram following the intravenous injection of double salts of antimony.<sup>6</sup>

Mainzer and Krause<sup>2</sup> who were the first to report significant electrocardiographic changes in man following tartar emetic, analyzed in detail the electrocardiograms of 12 Egyptian patients infected with *Schistosoma hematobium*, *Schistosoma mansoni*, or both. They were treated with a course

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of tartar emetic. The authors considered the electrocardiograms pathological in three of their cases, unaltered in three others and showing minor changes in the remainder. Most of the alterations were described in the T-waves and ST segments. They believed the extent of the changes was proportional to the bradycardia induced by antimony and regarded the results as an intoxication of the heart muscle, which in exceptional cases, might lead to "heart failure and death, probably through auricular fibrillation."

#### MATERIALS AND METHODS

In 200 of the 488 patients with an overseas diagnosis of *Schistosomiasis japonica*, electrocardiograms were taken shortly after admission to this hospital and from 22 to 162 days after the patients had completed treatment overseas. They had received variable amounts of fuadin, in 6 per cent solution, ranging from 10 to 109 c.c.—with an average dose of 40 c.c. Some had been given tartar emetic in doses comparable to those to be described under plan two below, and a small number had had both fuadin and tartar emetic.

The electrocardiograms were all within normal limits except in four instances. Two showed ventricular premature contractions from single foci. The third had low voltage T-waves in the standard leads with negative T-waves in all precordial leads. The fourth presented a short PR interval with a wide QRS complex (Wolff-Parkinson-White syndrome). Although the ova of *S. japonicum* may lodge in the myocardium and cause inflammatory reactions,<sup>7</sup> no clinical evidence of heart disease due to this condition was found in any of the patients. As a group they ranged from 20 to 40 years and represented an average cross section of previously healthy young soldiers who had been in the Pacific area under field or combat conditions for periods of several months to two years.

On the basis of overseas records and the findings at this hospital the diagnosis was confirmed by finding of ova in the stools in 80 per cent of the patients. In the other 20 per cent the diagnosis was justified on the history of exposure and clinical findings.<sup>1</sup> No patient was started on treatment at Harmon General Hospital unless ova were found in the stool.

The first 141 patients to be treated form the basis of this report. Each patient was observed for 90 days after treatment. If the stools became positive he was again treated and electrocardiograms recorded. Of the group, 35 patients required two courses of treatment and five patients required three courses during the period of observation which began in April and ended in November 1945.

The patients were divided into comparable groups to test the efficacy of fuadin, tartar emetic commercially prepared in ampoules, and tartar emetic freshly prepared. Since the frequency and degree of the changes induced in the electrocardiogram by both types of tartar emetic were the same, the patients who received this medication will be treated as one group.

Four plans of treatment were followed to determine the most effective course of therapy. In view of the importance of the dosage and frequency of injection of these drugs, it is necessary to consider in detail the several treatment plans employed.

*Plan 1.* A group of 33 patients were treated with fuadin given intramuscularly in 6 per cent solution. Each cubic centimeter was equivalent to 0.0087 gm. of antimony. The first three injections were 1.5 c.c., 3.5 c.c. and 5 c.c. on consecutive days. All subsequent injections were 5 c.c. given on alternate days until a total of 65 c.c. had been given in 25 days. Of this group, 25 patients required a second course of 65 c.c. of fuadin within 40 to 90 days. Following the second course at least five patients again showed the ova in their stools 30 to 60 days later. These were treated with tartar emetic, 416 c.c., as in plan four.

*Plan 2.* A group of 67 patients received tartar emetic intravenously in 0.5 per cent solution. Each cubic centimeter was equivalent to 0.0018 gm. of antimony. The first four injections were 8 c.c., 12 c.c., 16 c.c., and 20 c.c., given very slowly on alternate days. The fifth and all subsequent injections were 24 c.c. given in the same way for a total of 320 c.c. in 29 days. Of this group 10 patients required a second course of 320 c.c. of tartar emetic within 60 to 90 days.

*Plan 3.* A group of 15 patients received 105 c.c. of fuadin in a manner similar to plan one for 41 days.

*Plan 4.* A group of 31 patients received 416 c.c. of tartar emetic in 0.5 per cent solution as in plan two for 39 days. In this group are included five patients who had failed of cure in their second course of treatment with 65 c.c. of fuadin.\*

Every patient had at least one electrocardiogram prior to treatment. This served as a control from which all subsequent changes were noted. There was also an electrocardiogram 30 to 60 days after completion of treatment, to determine the time of return to normal. This tracing served as an additional check on the normal when a second course of treatment was necessary.

Early in the study the electrocardiograms were taken on an amplifier tube type of apparatus (General Electric) and on the hospital model string instrument (Cambridge). It was soon evident that comparison of tracings taken on these two machines was difficult and inclined to be inaccurate due

\* The following table gives the conversion values of c.c. of fuadin or tartar emetic to gm. of antimony as employed in this study.

Fuadin	c.c.	10	20	45	50	65	80	105
	gm.	.087	.174	.392	.435	.566	.696	.913
Tartar Emetic	c.c.	20	80	128	176	248	320	416
	gm.	.036	.144	.230	.317	.446	.576	.743

to variations in the height of the complexes, despite adequate standardization. All records subsequently were taken on the string instrument.

All tracings were taken under standard conditions, usually one hour after injections, with the patient lying in a comfortable prone position. The precordial lead was  $CF_4$ . In several instances in which abnormal findings were recorded in this lead, additional leads— $CF_1$ ,  $CF_2$ ,  $CF_3$ , and  $CF_5$ —were taken.

Because of the uncertainty of the time of appearance of changes in the electrocardiogram during treatment with the two drugs, frequent records were taken in the early phases of the study, including tracings immediately and one hour after injection, in the case of tartar emetic.

Patients receiving 65 c.c. of fuadin had records taken after 5 c.c., 45 c.c., and 65 c.c. of medication. Later in the study, the electrocardiogram after the 5 c.c. dose was discontinued. Patients receiving 105 c.c. of fuadin had tracings recorded after 50 c.c., 80 c.c., and 105 c.c.

In the tartar emetic group, electrocardiograms were taken after 80 c.c., 248 c.c. and 320 c.c. of medication. Later this was changed to 176 c.c. or 200 c.c. and 320 c.c. In those receiving 416 c.c., an electrocardiogram was recorded after this dose in addition to the others.

In a few individuals who showed marked changes in the electrocardiogram, special studies were made, including daily records. In all, about 900 electrocardiograms were read and compared by one observer. Each tracing was analyzed for rate, PR interval, alterations in form and height of P, QRS and T-waves. In representative groups detailed measurements of QRS width and QT intervals were tabulated in the serial records.

## FINDINGS

The alterations in the electrocardiograms were, for the most part, confined to the T-waves. To simplify description and analysis, the changes in the T-waves have been classified from one to four plus based upon the following criteria (figures 1 to 4):

1. One plus change was equivalent to a decrease of 30 to 50 per cent in the T-wave voltage in two or more leads.

2. Two plus change represented a further decrease in T-wave voltage with a lengthening of the proximal slope and a rounding of the summit of the waves in two or more leads.

3. Three plus change was a continued decrease in the height of the T-waves to extremely low voltage or isoelectric levels in three or more leads, accompanied by a slight negativity of the terminal portion in one or more of the leads. The summits of the waves presented no sharp angles, but were rounded or flattened.

4. Four plus change represented an alteration from positive T-waves to sharply negative or even cove plane T-waves in three or more leads, with low voltage in the remaining lead.

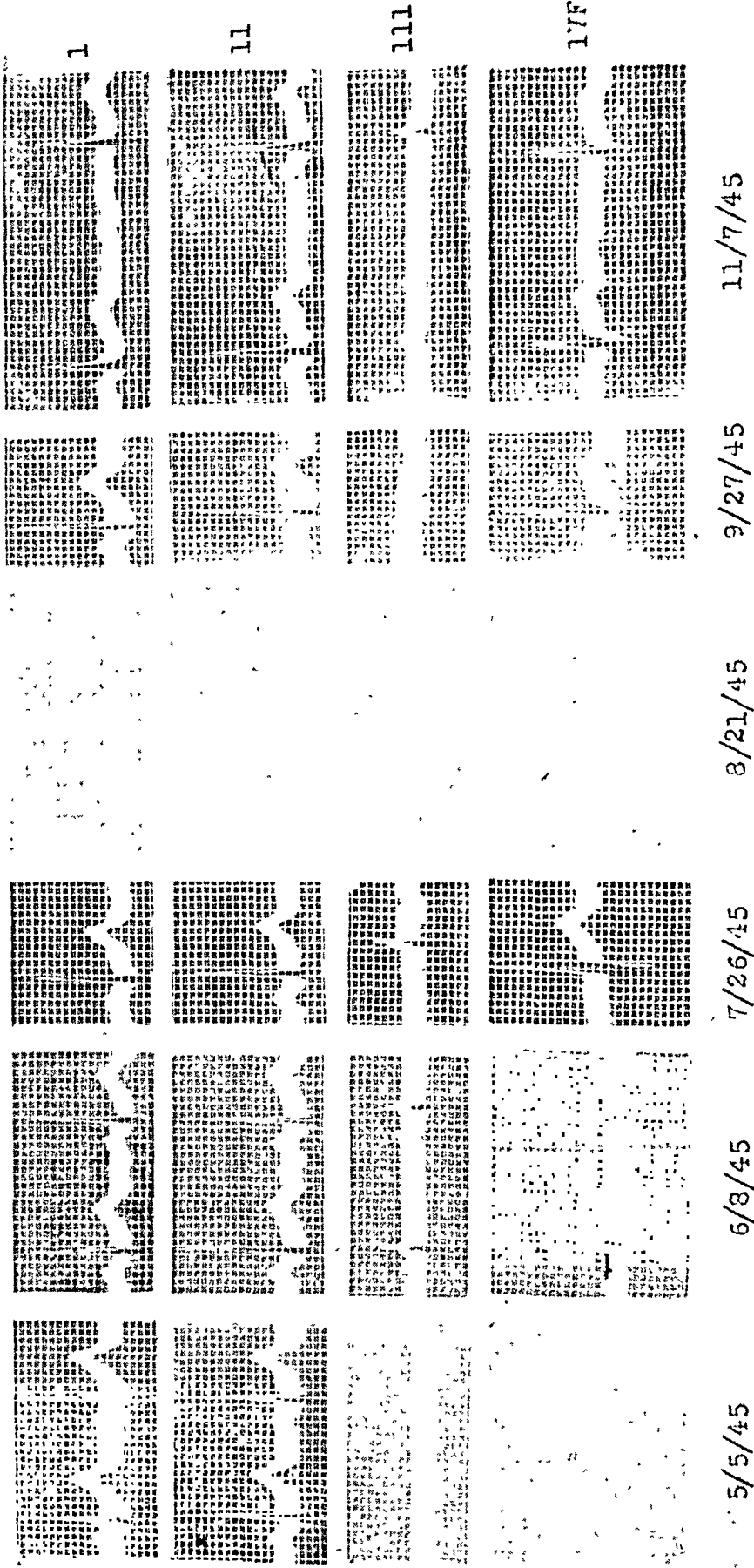


FIG. 1. R. C. 23 year old male with schistosomiasis. One plus change in T-waves produced during treatment with two successive courses of 65 c.c. of fuadin in 6 per cent solution (equivalent to .566 gm. antimony in each course) and one course of 416 c.c. of tartar emetic in .5 per cent solution (equivalent to .743 gm. antimony).

5/5/45—Control record 94 days after treatment with 40 c.c. of fuadin overseas.  
 6/8/45—One plus change after first course of 65 c.c. of fuadin.  
 7/26/45—Return to control level 48 days after treatment.  
 8/21/45—One plus change after second course of 65 c.c. of fuadin.  
 9/27/45—Return to control level 37 days after treatment.  
 11/7/45—One plus change after 416 c.c. of tartar emetic.

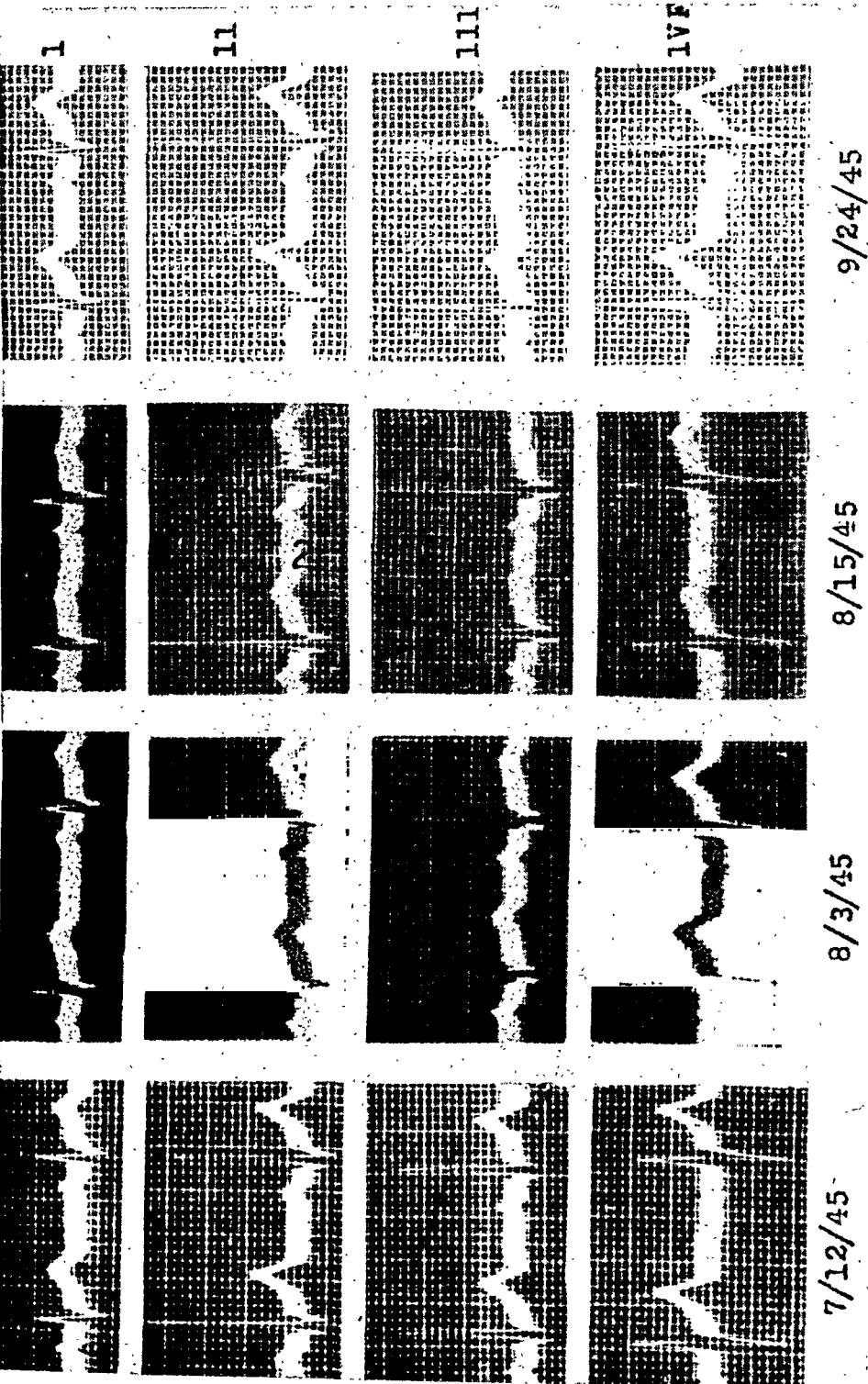


FIG. 2. P. B. 21 year old male with schistosomiasis. Two plus changes in T-waves produced during treatment with 320 c.c. of .5 per cent solution of tartar emetic (equivalent to .576 gm. of antimony).  
7/12/45—Control record 121 days after treatment with 40 c.c. of fuadin (.348 gm. antimony) overseas.  
8/3/45—One plus change after 176 c.c. of tartar emetic.  
8/15/45—Two plus change after 320 c.c. of tartar emetic.  
9/24/45—Return to control level 40 days after treatment.

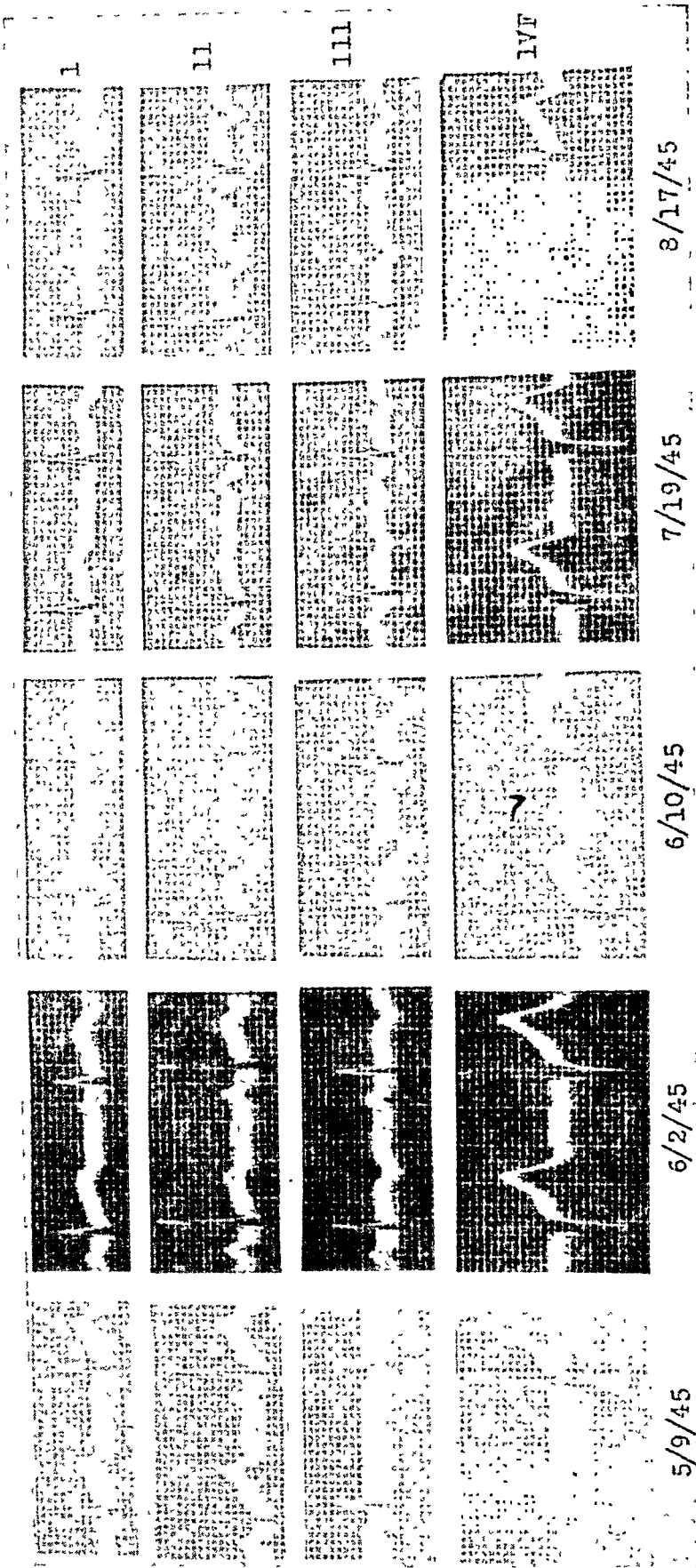


Fig. 3. W. K. 29 year old male with schistosomiasis. Three plus change in T-waves produced during treatment with two successive courses of 65 c.c. of fuadin in 6 per cent solution (equivalent to .566 gm. antimony) followed by (figure 3A) four plus changes during a course of 416 c.c. of tartar emetic in .5 per cent solution (equivalent to .743 gm. antimony).

5/9/45—Control record 32 days after treatment with 40 c.c. of fuadin overseas.  
6/2/45—Two plus effect after 45 c.c. of fuadin.  
6/10/45—Three plus effect after 65 c.c. of fuadin.  
7/19/45—Two plus change still present 39 days after treatment.  
8/17/45—Three plus change after second course of 65 c.c. fuadin.

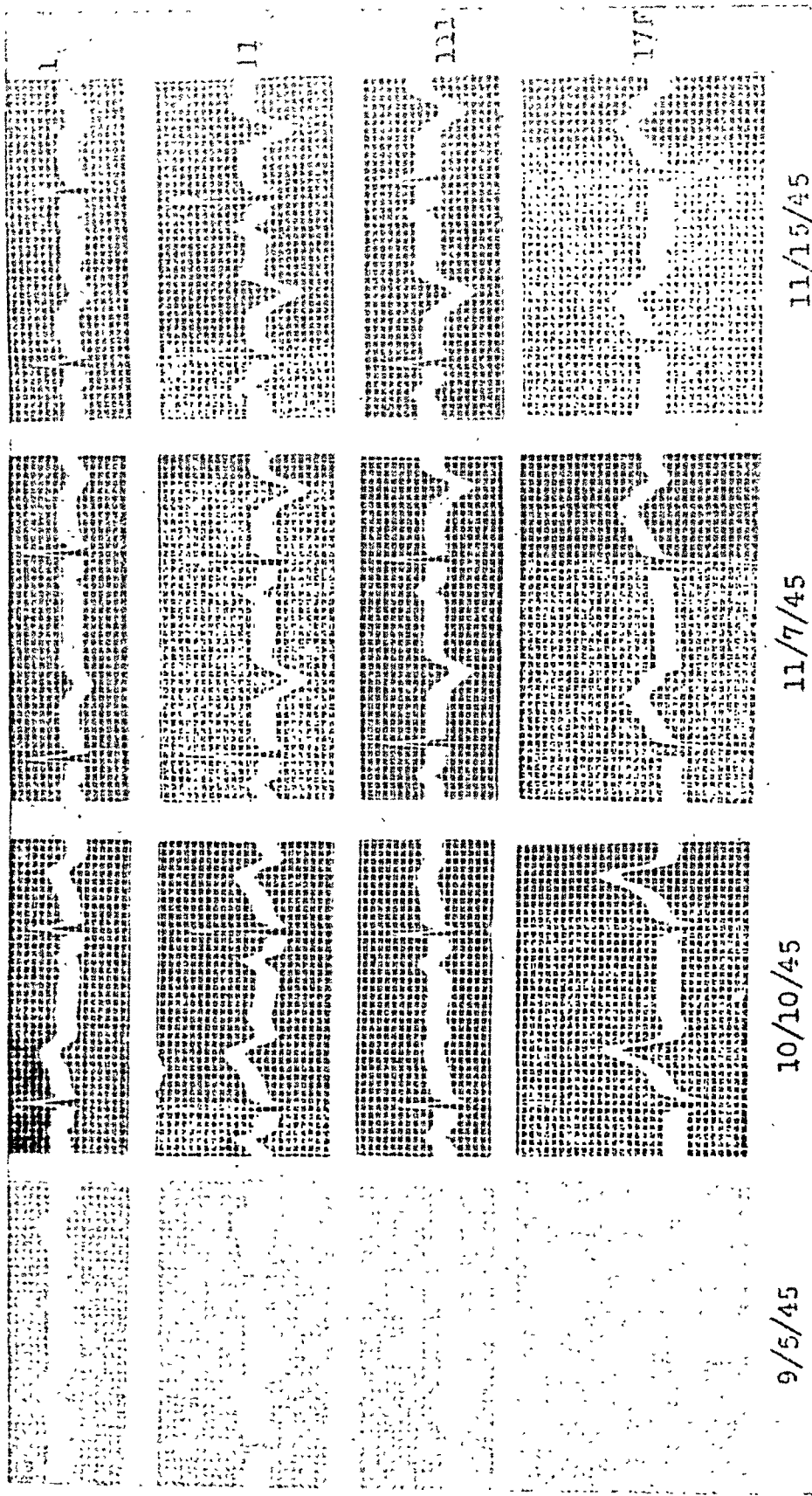


Fig. 3 A. Same patient as in figure 3.  
9/5/45—One plus effect still present 19 days after second course of treatment.  
10/10/45—Return to control level 54 days after second course of fuadin.  
11/7/45—Four plus effect after 320 c.c. of tartar emetic.  
11/15/45—Four plus effect unchanged after 416 c.c. of tartar emetic.



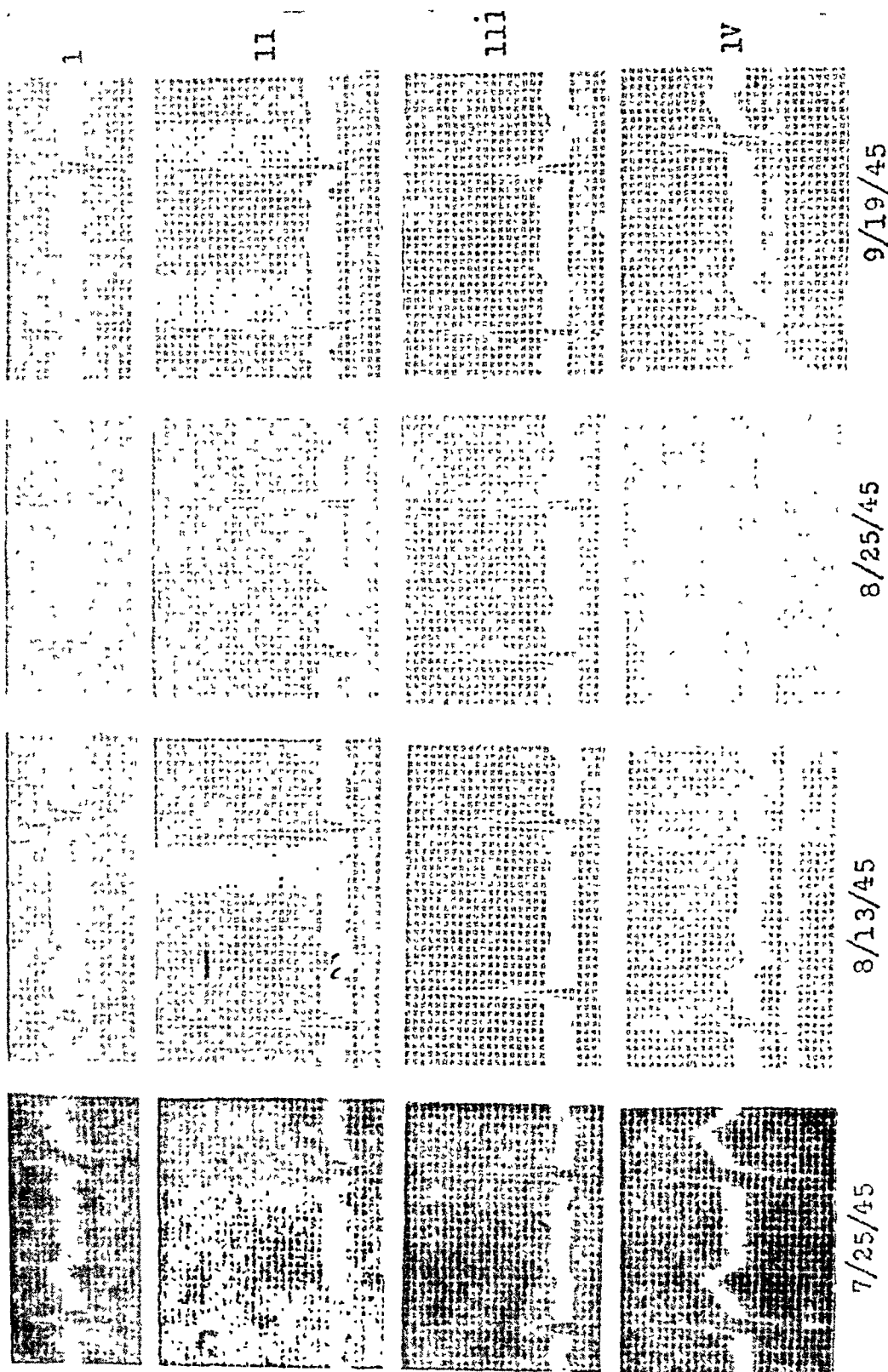


FIG. 4. B. K. 23 year old male with schistosomiasis. Four plus change in T-waves produced during treatment with 320 c.c. of tartar emetic in .5 per cent solution (equivalent to .576 gm. antimony).  
 7/25/45—Control record 162 days after treatment with 320 c.c. tartar emetic over seas.  
 8/13/45—Four plus effect after 176 c.c. of tartar emetic.  
 8/25/45—Four plus change more pronounced after 320 c.c. of tartar emetic.  
 9/19/45—Two plus change still present 25 days after treatment.

About 5 per cent of the records were difficult to classify in the above groups. They were considered with the group showing the lesser changes. When the control tracing showed a negative or diphasic T-wave, usually in Lead III, the change under medication was a further decrease in negativity. In the one patient previously mentioned whose control tracings showed low voltage T-waves in the standard leads and negative T-waves in all precordial leads, the alteration under tartar emetic was graded one plus and consisted of a slight negativity of T-waves in Leads I, II, III and a further increase in the depth of  $T_4$ . No definite heart disease could be established clinically in this patient.

In one patient who was treated with 416 c.c. of tartar emetic, as in plan four, all precordial T-waves developed a marked rounding of their summits and a widening of their bases without change in the height of the waves. The QT interval increased from .36 to .56 second with a decrease in rate from 68 to 62 per minute. The P-waves in Leads II and III were also altered (figure 5).

TABLE I  
Frequency of Lead Involvement

Leads Involved	Tartar Emetic	Fuadin	Total	
			Number	Per Cent
I, II, III, IV	57	18	75	56
I, II, IV	26	11	37	28
I, II, III	13	4	17	13
I, II	1	1	2	1.5
II, IV	1	0	1	.7
II, III, IV	0	1	1	.7
Total	98	35	133	

Table 1 indicates the frequency with which the different leads were affected and the combinations of leads involved in 133 patients. When changes in the T-wave occurred following administration of either fuadin or tartar emetic, 56 per cent of the tracings showed all four leads affected, 42 per cent showed three leads and 2 per cent showed only two leads.

Although in 98 per cent of the electrocardiograms showing changes, three or four leads were involved, the degree of alteration in each lead was not always the same. This is illustrated by those tracings in which the T-waves changed from positive to negative. Table 2 indicates the frequency pattern with which negative T-waves appeared in the different leads in records showing three to four plus changes. These tracings were obtained during 39 courses of treatment in 34 patients. The incidence of negative or diphasic T-waves in the control records is included. The most frequent combination occurred as a negative  $T_2$  and  $T_3$ . Lead III seemed to be the most sensitive to this type of change when the T-wave in only one lead became negative.

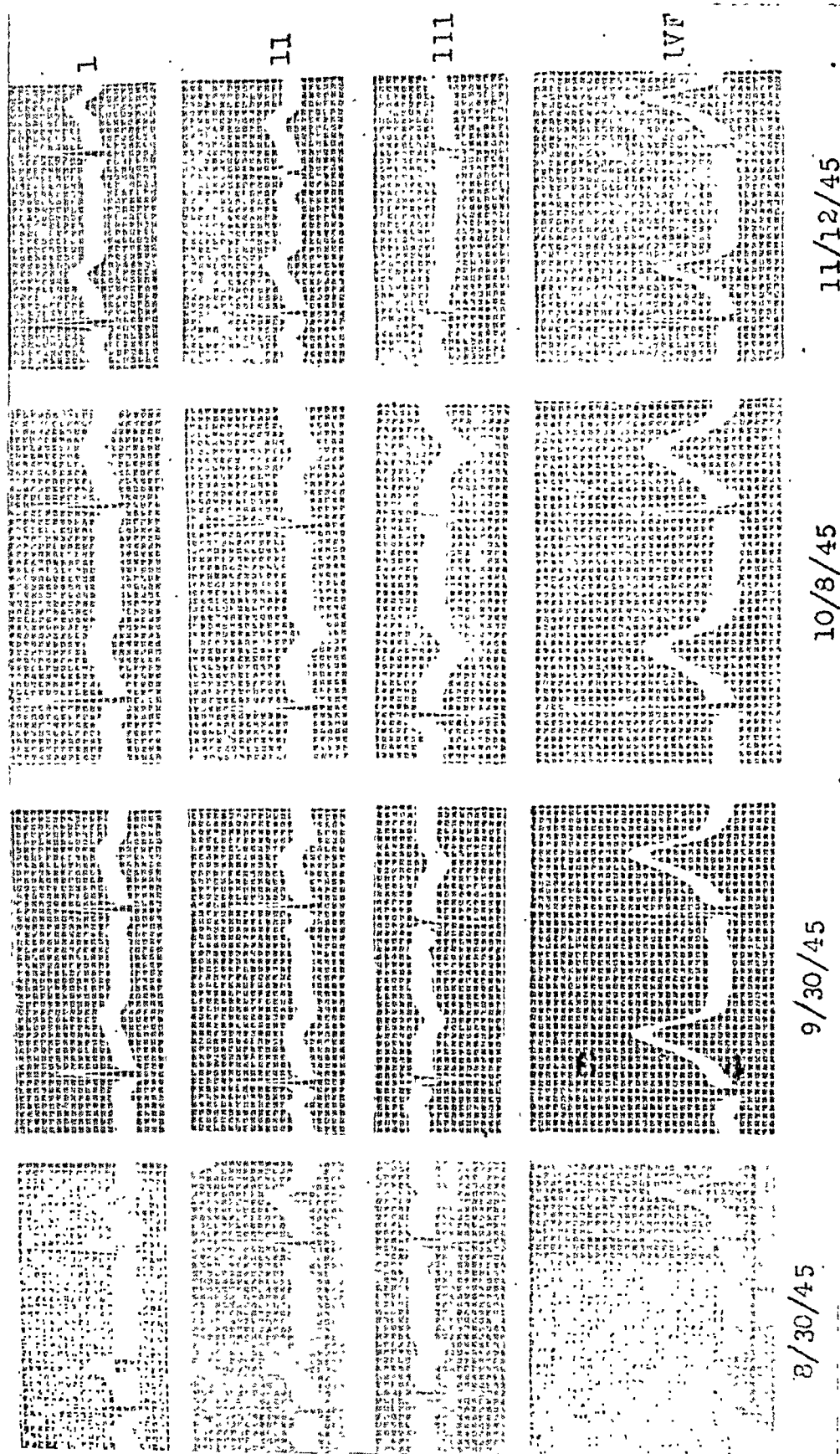


FIG. 5. J. H. 23 year old male with schistosomiasis. Three plus change in T-waves after 416 c.c. of .5 per cent solution of tartar emetic (equivalent to .743 gm. antimony). Unusually wide T-waves in precordial leads. QT interval prolonged.

8/30/45—Control record 120 days after treatment with 80 c.c. of fuadin overseas.

9/30/45—Two plus effect after 320 c.c. of tartar emetic.

10/8/45—Three plus effect after 416 c.c. of tartar emetic.

11/12/45—Slight change, one plus, still present 35 days after treatment.

TABLE II

Frequency of Negative T-Waves in Electrocardiograms Showing Three and Four Plus Changes during Treatment

Combination of Leads Involved	Frequency of Combination	Frequency of Negative or Diphasic T <sub>2</sub> in Control ECG
II, III	13	7
I, II, III, IV	6	5
III	6	0
II, III, IV	5	2
III, IV	4	1
I, IV	2	0
I, II, III	2	0
I, II	1	0

Elevation or depression of the RT or ST segment was not encountered in any of the groups. The proximal slope of the T-wave might change to become a long gradual slope or the wave flatten out completely, but it always arose from the base line. When the wave became negative and assumed a cove shape, the point of origin was still the isoelectric line, without elevation or depression of the point of origin.

Superficially, the negative T-waves resembled a coronary T-wave, but their origin and the slightly positive slope before the negative terminal portion helped to differentiate them. In some instances the terminal portion would become negative while the proximal portion was still quite rounded and several millimeters high. In succeeding tracings, following further medication, the height of the wave decreased and the terminal portion became more sharply negative and angular. A group of six patients was followed with frequent electrocardiograms, not more than a few days apart, after completion of treatment. The return of the T-waves to normal was in the reverse sequence of their production. They became less negative, slightly rounded and higher, and finally positive with sharp summits.

The T-wave changes in groups one and two plus were not striking and might have been considered within normal limits had no control tracings been available. In groups three and four plus the electrocardiograms were definitely abnormal and without cognizance of the effect of the medication could have been interpreted as showing evidence of myocardial damage.

Table 3 shows the frequency of changes encountered under the different plans of treatment. Every patient receiving a course of tartar emetic showed an alteration in his electrocardiogram. In 30 per cent of the patients these changes were in groups three and four plus and would be considered definitely abnormal. Only 6 to 14 per cent of the fuadin treated patients showed such marked changes.

When the treatment was repeated, the degree of electrocardiographic change was not significantly different in the second course of fuadin. Those showing no change or one plus remained the same. Four patients who previously showed no alteration now had one plus effect. In the five patients who were given 416 c.c. of tartar emetic, after two courses of 65 c.c. of fuadin, the patients all showed some degree of change. Table 4 shows

TABLE III

Distribution of the Degree of Change in the Electrocardiogram  
After a Course of Fuadin or Tartar Emetic

Drug	Total Antimony Grams	Total Cases	No Change		One Plus		Two Plus		Three Plus		Four Plus	
			No.	%	No.	%	No.	%	No.	%	No.	%
Fuadin 65 c.c.	.566	33	14	43	13	39	4	12	2	6	0	—
Fuadin 105 c.c.	.913	15	3	20	7	46	3	20	1	7	1	7
Tartar Emetic 320 c.c.	.576	67	0	—	27	40	20	30	16	24	4	6
Tartar Emetic 416 c.c.	.743	31	0	—	5	16	16	52	7	22	3	10

the degree of alteration in the electrocardiogram in two successive courses of treatment in 25 patients, and in three courses of treatment in five patients of the same group.

TABLE IV

Comparison of Degree of Change in the Electrocardiogram in Successive  
Courses of Treatment in 25 Patients

Case Number	First Course Fuadin 65 c.c.	Second Course Fuadin 65 c.c.	Third Course Tartar Emetic 416 c.c.
1	+	+	+
2	+	+	+
3	+	+	++
4	0	+	++
5	+++	+++	++++
6	++	++	
7	++	++	
8	++	+	
9	+++	++	
10	+	+	
11	+	+	
12	+	+	
13	+	+	
14	+	+	
15	+	+	
16	+	+	
17	0	+	
18	0	+	
19	0	+	
20	0	0	
21	0	0	
22	0	0	
23	0	0	
24	0	0	
25	0	0	

In 10 of the 67 patients who were treatment failures with 320 c.c. of tartar emetic, and who received a second course 30 to 60 days later, the degree of change in the individual patient was practically the same. Those who, in their first course showed minimal changes of one and two plus, continued to do so, and those who showed three or four plus remained the same.

Although the quantitative change in the electrocardiogram in the tartar emetic and fuadin groups was different, qualitatively the alterations encountered were identical. This is well demonstrated in a group of five patients who were treatment failures after the second course of 65 c.c. of fuadin. They were treated in their third course with tartar emetic 416 c.c. The degree of change with tartar emetic was slightly greater than with fuadin, but the alterations in the T-waves, as they developed under tartar emetic, were indistinguishable from those produced by fuadin (figures 1, 3, 3 A).

The amounts of medication required to produce alterations in the electrocardiogram have been analyzed for all four plans of treatment. From table 3 it is evident that within each treatment group the same amount of total medication induced a variable response in the electrocardiogram in different individuals. One plus alterations occurred with as little as 10 c.c. of fuadin, in three patients. As the medication was continued, two of these patients developed two plus changes after a total of 45 c.c. of fuadin. The electrocardiogram of the third patient showed no further change, even after 65 c.c. of fuadin. The average dose required to produce one plus change was about 45 c.c. and the largest dose was 105 c.c. The smallest dose necessary to induce a two plus effect was 45 c.c. and ranged up to 105 c.c. of fuadin. A three plus change occurred with as little as 50 c.c. and the same individual gave a four plus with 80 c.c. It was the only maximum effect seen with fuadin.

In the tartar emetic group the earliest changes were noted in several patients with as little as 20 c.c. Most patients required 80 c.c. to produce a one plus effect. The smallest dose necessary for a two plus change was 80 c.c. and ranged up to 416 c.c. One patient who exhibited a one plus change with 20 c.c., showed three plus with 80 c.c. and four plus with 128 c.c. It usually required from 176 c.c. to 416 c.c. of tartar emetic to induce a three plus change. Four plus alterations were seen with 176 c.c., 200 c.c., 320 c.c., and 416 c.c. in four different patients.

In addition to T-wave changes, other alterations of minor nature were noted. In two instances infrequent ventricular premature beats and in one instance A-V nodal beats developed during treatment with tartar emetic. Although these alterations may not be an effect of the medication, they were not present in the control tracings and disappeared after treatment. No other disturbance in rhythm was detected.

The heart rates in our patients as recorded in their electrocardiograms during treatment revealed no pronounced bradycardia. In three instances the rate was 56 to 58, compared to control values of 60 to 75 per minute.

Although the literature<sup>5,9</sup> accepts as a pharmacologic fact that antimony slows the heart rate, it was not a striking or constant phenomenon in our patients. The records in 181 courses of treatment were analyzed for changes in rate. In 56 courses there was no significant change after treatment. In 48, there was an increase in rate from six to 30 beats with an average of 10 to 15 beats per minute. In 77, there was a decrease in heart rate from six to 30 beats with an average of 10 to 15 beats per minute. There was no relationship of the T-wave changes to the alterations in the heart rate during treatment.

The P-waves were practically unchanged in the serial tracings. In four instances, two of which are mentioned in the text,  $P_2$  and  $P_3$  became isoelectric or negative.

The PR interval showed no constant or significant alterations during treatment. No value above .20 second was encountered. Minor prolongations from .16 to .18 or .20 second were seen in about 15 per cent of the patients, but its significance is doubtful.

Alterations in the shape and height of the QRS complex were conspicuously absent under all plans of treatment. It was remarkable that this portion of the electrocardiogram remained unchanged despite striking alterations in the T-waves.

The QT interval was measured and compared with the rate to determine any prolongation or shortening during treatment. The standard used was derived from the formula  $QT = 0.39 \sqrt{RR} \pm .04$  where RR represents the time interval between beats (8). The curves of this equation form a convenient method of plotting the changes. About 20 per cent of the tracings showed a slight to moderate prolongation of the QT interval. In all instances in which the prolongation occurred, it was due to the widening of the base of the T-wave and not the QRS complex. In two patients under treatment with fuadin, a prolongation was seen in tracings in which the T-waves were not altered sufficiently to meet a minimum or one plus change.\*

The reversible nature of the changes became apparent in the follow-up tracings after treatment. In six patients electrocardiograms were taken every few days after the course of fuadin or tartar emetic was completed. It was of interest to note that records taken several days later might show more change than those on the last day of therapy. The beginning of the return to normal could be detected as early as one week after treatment. In those showing only one plus changes there were several whose tracings, 10 to 14 days after treatment, were the same as their control. The majority of patients were not reexamined until they had returned from a furlough or leave, 30 or more days after a course of treatment. In 90 per cent of those receiving the short course of fuadin or tartar emetic the electrocardiogram was normal by the time the patient returned from furlough, 30 to 60 days later. The mean furlough time was 35 days. The remaining 10 per cent

\* Several records were encountered in which the QT interval of the control was longer than the normal limits. The change in these patients was a slight further prolongation under treatment.

at this time showed slight T-wave changes that were only significant when compared with the control and did not exceed those seen in our one plus group. It is worth noting that even in patients treated with the larger doses of fuadin or tartar emetic, the tracings in all but 10 per cent had returned to normal in 60 days.

In one patient who was treated with 65 c.c. of fuadin without any change in the electrocardiogram, an unusual alteration was present on his return from furlough 38 days later. The electrocardiogram showed negative T-waves in all leads equal to four plus changes.  $P_2$  and  $P_3$  were negative. The following day the P-waves were normal without any change in the T-waves. Within five days the T-waves showed definite indications of returning to the normal pattern. At the end of 38 days, or 76 days after treatment, they were equal to the control except for slight rounding and lowering of  $T_2$ . This patient did not require a second course of treatment and afforded no opportunity to check this behavior of his electrocardiogram.\*

In seven patients who showed T-wave changes of varying degree during treatment, electrocardiograms were taken 30 minutes after 1 mg. of atropine sulfate subcutaneously. The rate increased but there was no effect on the T-waves.

During the course of treatment with tartar emetic, and to a lesser degree with fuadin, the patients develop minor toxic symptoms such as cough, muscle and joint pains, and nausea. The changes in the electrocardiogram showed no relationship to these minor toxic symptoms. Those who exhibited three and four plus alterations had no greater incidence of these complaints than did the patients with one or two plus changes.

### DISCUSSION

Both fuadin and tartar emetic are compounds of trivalent antimony. The toxicity of trivalent antimony preparations is probably related to the liberation of the inorganic antimony from the complex molecule.<sup>9, 10</sup> Although the total antimony in both drugs, as given under treatment plans one and two, was almost equal in amount, the changes induced in the electrocardiogram by tartar emetic were more common and of greater degree. This may be related to the ease with which antimony is liberated from the respective compounds.

In view of the response to trivalent antimony preparations, it was desirable to determine the effect of pentavalent compounds on the electrocardiogram. No references to such studies were found. Leishmaniasis is treated by pentavalent antimony preparations such as neostam and neostibosan. In three American soldiers who contracted the disease in India, treatment at this hospital consisted of an intravenous course of neostam equal to 4.7 gm. in one patient, and neostibosan equal to 5 gm. in the other two. The total amounts of pentavalent antimony injected were equivalent to 1.41

\* He was questioned closely concerning the possibility of treatment by antimony medication during his furlough, but denied receiving any. Clinically he was well and had no abnormal cardiovascular findings.



and 2.10 gm. respectively. No effect on the electrocardiogram was noted. A much larger group will have to be evaluated to determine the effect of pentavalent antimony.

Khalil<sup>11</sup> states that individual variations occur in the excretion of antimony. This, he believes, explains the variation in therapeutic response and tolerance. The absorption of fuadin, following intramuscular injection, is very rapid.<sup>9</sup> The excretion begins within 24 hours and may continue for two months or more after a course of treatment.<sup>5</sup> The rate of disappearance of tartar emetic from the bloodstream after injection is probably rapid. In the rabbit it is within 30 minutes.<sup>12</sup> Both tartar emetic and fuadin yield antimony, which is deposited in body tissues. Chemical analysis of tissues taken from a child who died during fuadin therapy indicates that the liver stores a large amount of antimony.<sup>11</sup> In experiments of chronic poisoning of rats and rabbits with tartar emetic over several months, the heart muscle was found to store a proportionate share of antimony.<sup>13</sup>

The selective action of these drugs upon the T-wave, without any significant effect on the other components of the electrocardiogram, leads one to the conclusion that the response noted is due to alterations in the electrical activity of the ventricle. This alteration is probably due to a temporary deposition of antimony in the heart muscle.

The similar changes in the electrocardiogram on repeated courses of fuadin or tartar emetic may be explained by the relative constancy, in any given individual, of the several factors in the body metabolism, which would affect the deposition of antimony. In several of our patients who received repeated courses of fuadin and tartar emetic the changes in the T-waves, in the individual patient, were observed to be identical even in the minor details.

It is possible that variations in deposition and mobilization of antimony, in some patients, may lead to a higher concentration in the heart for several days after treatment is completed. This would explain the behavior of those patients whose electrocardiograms showed greater change several days after treatment than at the time of completion of treatment. The gradual return of the electrocardiogram to normal over a period of 30 to 60 days, following treatment, is in keeping with the known slow excretion of antimony.

The variable dose required to produce the electrocardiographic changes and the lack of additional response in some patients despite continuation of the drug, suggests a balance may have been effected between storage and excretion, to keep the amount in the heart relatively constant. It is not known how much antimony is actually deposited in the heart muscle and what amounts are needed to produce alterations in the electrocardiogram. An average dose of .392 gm. of antimony as fuadin, or .144 gm. of antimony as tartar emetic was required to produce a one plus effect. With such small doses, the amount of antimony stored in the heart must necessarily be still smaller.

The possible relationship of the level of blood antimony to the production of electrocardiographic changes has been considered. From what is known

of the behavior of the group of heavy metals, viz., bismuth, mercury, arsenic, and lead, to which antimony is related, storage in tissues, rather than transient blood level determines the pharmacologic action. The time of appearance and regression of the electrocardiographic alterations is much more in keeping with a storage rather than blood level effect of antimony.\*

It may be questioned whether the effects on the electrocardiogram were not due to the whole molecule of fuadin or tartar emetic, or possibly to the potassium ion in the tartar emetic. The similarity of the changes induced by the two drugs speaks for a common origin. Fuadin is a sodium salt of antimony which would suggest that potassium is not a factor. Furthermore, the electrocardiographic changes following potassium intoxication are entirely different. The occurrence of the same qualitative changes in five patients treated with fuadin and tartar emetic successively, again argues for a common denominator of antimony.†

### SUMMARY

1. The trivalent compounds of antimony, fuadin and tartar emetic, employed in the treatment of 141 patients with proved *Schistosomiasis japonica* were found to produce significant changes in the electrocardiogram.

2. These changes were confined to the T-waves and have been quantitatively graded. Records exhibiting the more marked changes, could, without cognizance of the medication, have been interpreted as showing evidence of myocardial damage.

3. In every patient receiving tartar emetic changes were induced in the electrocardiogram. In 57 per cent to 80 per cent of those receiving fuadin, depending on the dosage, similar alterations were found.

4. These changes were of a reversible nature and disappeared within 30 to 60 days after treatment was completed in 90 per cent of the patients. There were no cardiovascular symptoms accompanying them.

5. In repeated courses with the same compound, a similar degree of change was elicited. The alterations produced represent an individual response and are probably associated with the storage of antimony in the heart.

6. The changes induced were of such definite and distinct pattern that in the more marked alteration they may, within the limitations of our present knowledge, be recognized as a specific effect of antimony.

### BIBLIOGRAPHY

1. MASON, P. K., DANIELS, W. B., PADDOCK, F. B., and GORDON, H.: Studies on *Schistosomiasis japonica*: The latent phase of *Schistosomiasis japonica*. To be published.
2. MAINZER, F., and KRAUSE, M.: Changes of the electrocardiogram appearing during antimony treatment, Trans. Roy. Soc. Trop. Med. and Hyg., 1940, xxxiii, 405.

\* In selected patients, blood antimony levels, and the excretion of antimony in urine and stool, have been followed during and after treatment. The results of this work will be reported at a later date. (Unpublished data; Lippincott, S. W., Ellerbrook, L. E., Rhees, M., and Paddock, F. B.)

† No data are available on the effect of sodium antimony tartrate upon the electrocardiogram. Its use in small series would eliminate the question of potassium effects.

3. TARR, LEONARD: The effect of the antimony compounds, fuadin and tartar emetic, on the electrocardiogram, Bull. U. S. Army Med. Dept., 1946, v, 336.
4. (a) KHALIL, M.: The specific treatment of human schistosomiasis, Arch. f. Schiffs. u. Trop. Hyg., 1931, xxxv. Quoted by.<sup>5</sup>  
(b) Ibid., Jr. Egyptian Med. Assoc., 1936, xix, 285. Quoted by.<sup>2</sup>
5. SCHMIDT, H., and PETER, F. M.: Advances in the therapeutics of antimony, 1938, George Thieme, Leipzig, Germany. Reproduced by Alien Property Custodian, 1944, published by J. W. Edwards.
6. MASSON, G. A.: The action of bismuth on the circulatory system, Jr. Pharmacol. and Exper. Therap., 1926, xxx, 39.
7. AFRICA, C. M., and SANTA CRUZ, J. L.: Eggs of *Schistosoma japonicum* in the human heart. Vol. Jubilaré Pro. Prof. Sadao Yoshida, Osaka, 1939, ii, 113.
8. HEGGLIN, R., and HOLZMANN, M.: Die klinische Bedeutung der verlängerten QT-Distanz (Systolendauer) im Elektrokardiogramm, Ztschr. f. klin. Med., 1937, cxxxii, 1.
9. GOODMAN, L., and GILMAN, A.: The pharmacologic basis of therapeutics, 1941, The Macmillan Co., N. Y.
10. WEESE, H.: Important pharmaceutical aspects of solustibosan, Chinese Med. Jr., 1937, lii, 421. Quoted by.<sup>5</sup>
11. KHALIL, M.: Excretion of drugs: its influence on therapeutic results with special reference to antimony treatment of schistosomiasis, Lancet, 1936, ccxxxi, 132.
12. LUCIA, S. P., and BROWN, J. W.: Effects of potassium antimonyl-tartrate on blood and hematopoietic organs, Jr. Pharmacol. and Exper. Therap., 1934, lii, 418.
13. BRADLEY, W. R., and FREDRICK, W. G.: The toxicity of antimony, Indust. Med., 1941, x, 15.

# STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS IN HUMANS

## II. PULMONARY TUBERCULOSIS \*

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### INTRODUCTION

IN a preceding paper,<sup>1</sup> observations on the streptomycin treatment of meningeal and generalized hematogenous tuberculosis were presented. On the basis of these studies and in confirmation of the previous reports of Hinshaw and Feldman,<sup>2,3</sup> it was concluded that streptomycin is capable of exerting a powerful effect upon the course of tuberculous infections in humans. It was further concluded<sup>1</sup> that in miliary tuberculosis, at least, the development of streptomycin-resistance as detected in vitro, reflects the presence of a drug-resistant infection in vivo.

The present report is concerned with the results observed in 43 patients with pulmonary tuberculosis who received streptomycin on the Cornell-New York Hospital Medical Service during the 19 month period, January 1, 1946 to July 31, 1947. Only those patients, 36 in number, who have been observed for a minimum period of six weeks following the completion of the streptomycin therapy are considered in detail (table 1).

*Outline of the Investigation.* All of the patients were confined to bed during therapy and in the post-treatment period. They were permitted to sit up in bed but were not usually allowed bathroom privileges. No form of collapse therapy was induced in any patient until at least 90 to 120 days had elapsed since the start of antimicrobial therapy.

The type of streptomycin used, the intervals at which the appropriate clinical and roentgenologic examinations were made, and the technics employed in the bacteriologic studies are recorded in a previous communication.<sup>1</sup>

*Streptomycin Regimens.* In the first part of the investigation, all of the patients received 3.0 grams of streptomycin daily, administered intramuscularly in divided

\* Portions of this study were presented before the annual meetings of: the American College of Physicians, Chicago, April 29, 1947; the American Society for Clinical Investigation, May 5, 1947; and the Section on Internal Medicine of the American Medical Association, June 12, 1947.

From the Department of Medicine of the New York Hospital-Cornell University Medical College.

The first part of this investigation was conducted under the direction of the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman. The subsequent investigation is a part of the Streptomycin Manufacturers American Trudeau Society program which is being conducted in collaboration with the Tuberculosis Study Section of the National Institute of Health. The streptomycin was furnished by the Chemotherapeutic Committee; by a generous donation from Charles Pfizer and Company, Inc., Brooklyn; and from supplies donated to the American Trudeau Society by the Streptomycin Manufacturers.

The study was aided in part by grants from the National Institute of Health, and from the Lederle Laboratories, Inc., Pearl River, New York.

TABLE I

Classification According to Clinical Type and Presumed Pathological Character of 36 Cases of Pulmonary Tuberculosis. Each Followed for at Least Six Weeks after Completion of Streptomycin Therapy

Clinical Type (and presumed pathological character)	No. of Cases	Cavity Closure	Sputum Conversion
Group I. <i>Early Predominantly Exudative</i> , with recent excavation			
(a) Patchy pneumonic (with annular, thin-walled cavities)	11	7	6
(b) Confluent pneumonic (with consolidation but little excavation)	3	2	2
(c) Progressive primary (with cavitation)	1	1	1
(d) Caseo-cavernous (with massive caseation and large or multilocular cavities but little evidence of fibrosis)	3	0	0
Group II. <i>Chronic Type</i> , with fibro-cavernous secondary changes.	18	3	5
Total	36	13	14
Far advanced	25		
Moderately advanced	11		

doses for a total period of 120 days. The 120 day regimen was selected arbitrarily in an effort to provide antimicrobial therapy for the longest period which was thought to be generally feasible. After 18 patients had been treated, the total period of treatment was shortened to 42 days in an effort to avoid the production of streptomycin-resistant strains of tubercle bacilli.

When preliminary studies of Pfuetze<sup>4</sup> and Hinshaw<sup>5</sup> indicated that the administration of one gram of streptomycin daily in divided doses appeared therapeutically satisfactory and definitely less toxic, the daily dose used in the present study was lowered to one gram administered in a single injection. Only 10 individuals with pulmonary tuberculosis have completed therapy on the one gram-42 regimen and only three among the 36 listed in table 1. It is not possible, therefore, to compare the therapeutic effectiveness of this regimen with the results observed following the use of the three gram daily dose. There is definite evidence, however, that the neurotoxicity of the one gram daily dose is considerably less than is observed with the larger doses. Only one of 10 patients who have completed the one gram-42 day regimen have either subjective or objective evidences of vestibular dysfunction. In contrast, this reaction was observed uniformly in the patients who received the 3.0 gram daily dose for a comparable period.

*Types of Pulmonary Tuberculosis.* A classification of the 36 completed cases, on the basis of clinical type and presumed pathologic character of the disease, is presented in table 1. All cases were of moderately or far advanced extent. One case in a child is listed as of progressive primary type, although the disease differed little from several cases of predominantly lower lobe distribution in adults. All of the patients had progressive lesions and tubercle bacilli were readily demonstrated in the sputum of all. One or more areas of pulmonary excavation were demonstrable in all but two of the cases, both of which were far advanced in extent. In six there were concomitant ulcerative lesions of the larynx or bronchi.

## OBSERVATIONS AND RESULTS

*Group I. Early Predominantly Exudative Tuberculosis with Recent Excavation.* Eighteen patients with disease of predominantly exudative character and in whom the greatest part of the pulmonary involvement was known to be recent\* were treated. All but one received three grams of streptomycin daily. The results after completion of the antimicrobial therapy in the several types of cases in this group are shown in table 1 (group I).

In general, there was a measurable improvement by recognized criteria during the first six weeks of streptomycin therapy. The degree of change depended to a considerable extent upon the severity of the disease when treatment was started. Thus the amount of subjective and objective improvement was usually much more pronounced in the patients with large areas of confluent pneumonia than in those who had patchy pneumonic lesions with thin-walled cavities. Several in the latter group were afebrile and essentially asymptomatic before institution of the antimicrobial therapy.

Definite clinical improvement of some degree, however, was noted in all patients who had symptoms at the start of therapy. In some instances, the speed with which a striking degree of improvement appeared was comparable to the rapid changes observed in the streptomycin treatment of hematogenous tuberculosis. Defervescence within one week after the start of antimicrobial therapy was observed in seven of the eight patients with exudative lesions whose daily temperatures before treatment had consistently attained 102° F. In addition to the high incidence of temperature defervescence, virtually all of the patients experienced a conspicuous reduction in cough and expectoration and an appreciable gain in weight and in strength.

A change in the character of the physical signs in the chest was frequently noted as early as two weeks after the start of streptomycin therapy. In the confluent pneumonic type (group Ib, table 1) with signs predominantly those of consolidation rather than of cavitation the regression of signs was characterized by reduction in the area over which dullness, bronchial breath sounds and bronchophony were elicited as well as by a striking reduction in the number of râles. The former signs disappeared entirely in one case. In the cases with mixed signs of consolidation and excavation (group Id, table 1) the changes were less conspicuous and a relatively large area of bronchial or amphoric breath sounds persisted. In the type of patchy pneumonic lesion (group Ia, table 1) in which the presence of râles was often the only detectable physical sign, a disappearance or diminution in the number of râles was frequently observed during the first six weeks of streptomycin therapy.

With but a few exceptions, the major part of such clinical improvement as occurred was completed within the first four to six weeks of antimicrobial therapy. Roentgenologically detectable changes also appeared during this

\* In all instances less than three months old, by evidence of prior roentgenograms or, as in several of the fulminating types, by history of acute symptomatic onset.

period and continued thereafter as is described below. After the initial improvement, these predominantly exudative cases followed one of several patterns:

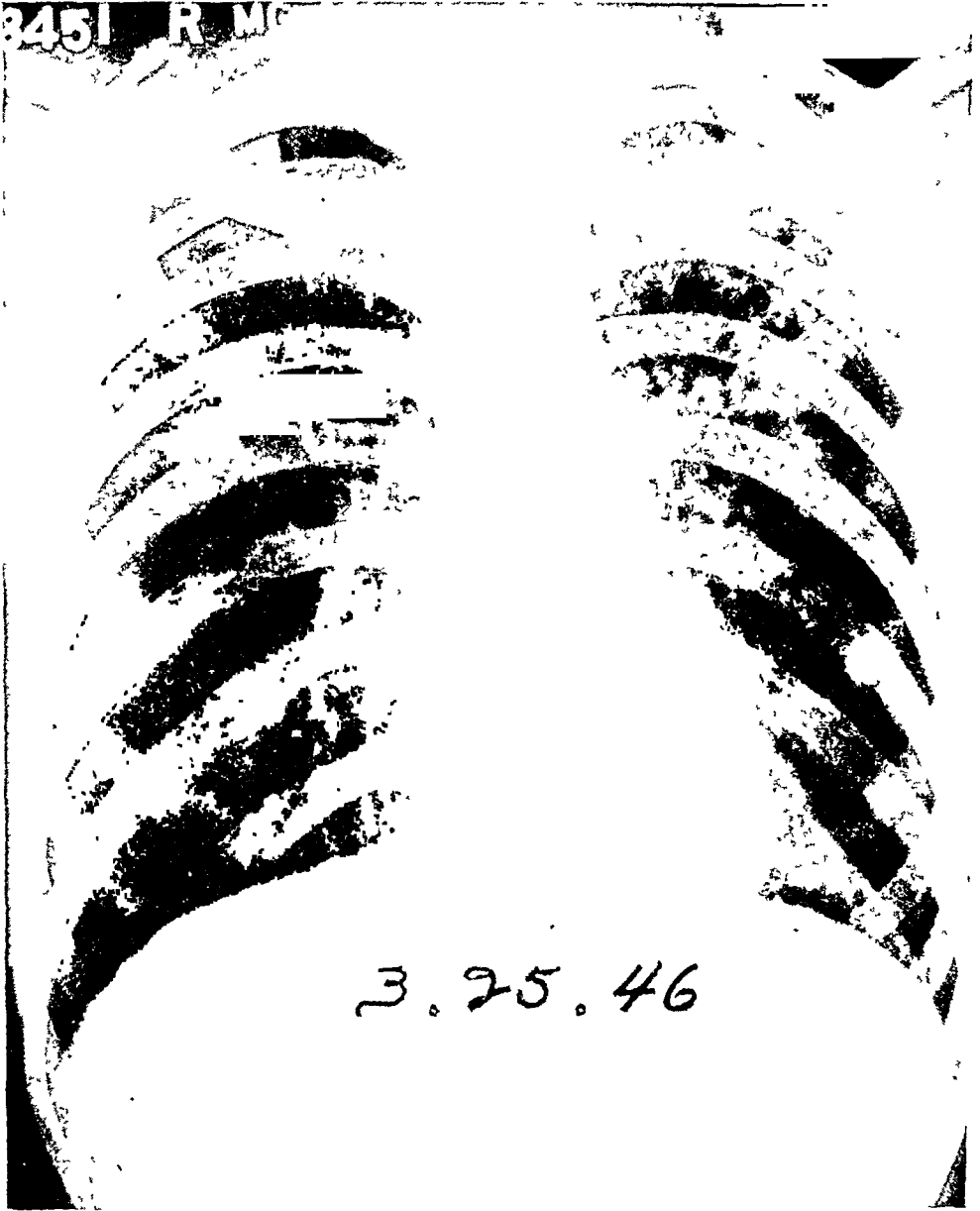


FIG. 1a. Patient C.Ya. Twenty-four year old Chinese man. Symptoms of cough, recurrent small hemoptyses and low grade irregular fever for  $2\frac{1}{2}$  months. Roentgen-ray of lungs before streptomycin treatment. Note thin walled cavity in left infraclavicular region and surrounding patchy pneumonic infiltration. Shadows stationary during one month of observation on bed rest before treatment.

(1) Continued quiescence with extensive roentgenologic clearing, cavity closure and sputum conversion. Three of nine such cases, however, relapsed after several months.

(2) Continued quiescence with a variable degree of roentgenologic clearing and cavity reduction but without complete closure or disappearance of bacilli from the sputum.

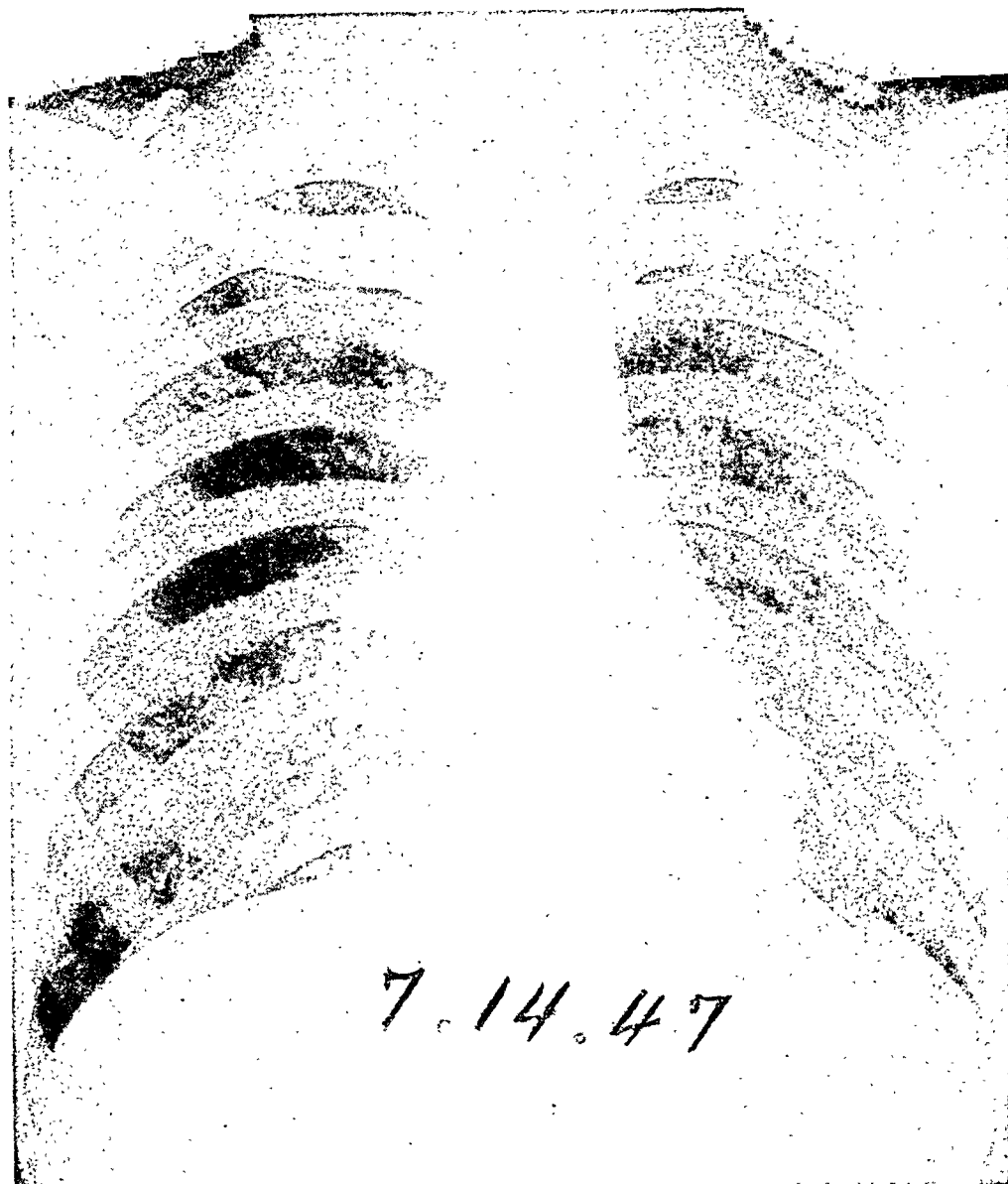


FIG. 1b. Patient C.Ya., 16 months later. Closure of cavity took place within 6 weeks of beginning treatment. Infiltration had regressed extensively within 120 day period of streptomycin administration. Dose 3.0 gm. daily.

(3) A variable degree of symptomatic improvement accompanied by clinical and roentgenologic evidence of continued excavation with resumption of progressive course. The latter phase was usually preceded or accompanied by the appearance of organisms resistant to streptomycin in vitro.

*Continued Quiescence with Cavity Closure (Early Remission).* In nine



of the 18 patients with predominantly exudative lesions, there was extensive clearing of the infiltrative process, with cavity closure\* and sputum conversion during streptomycin therapy or in the immediate post-treatment period.

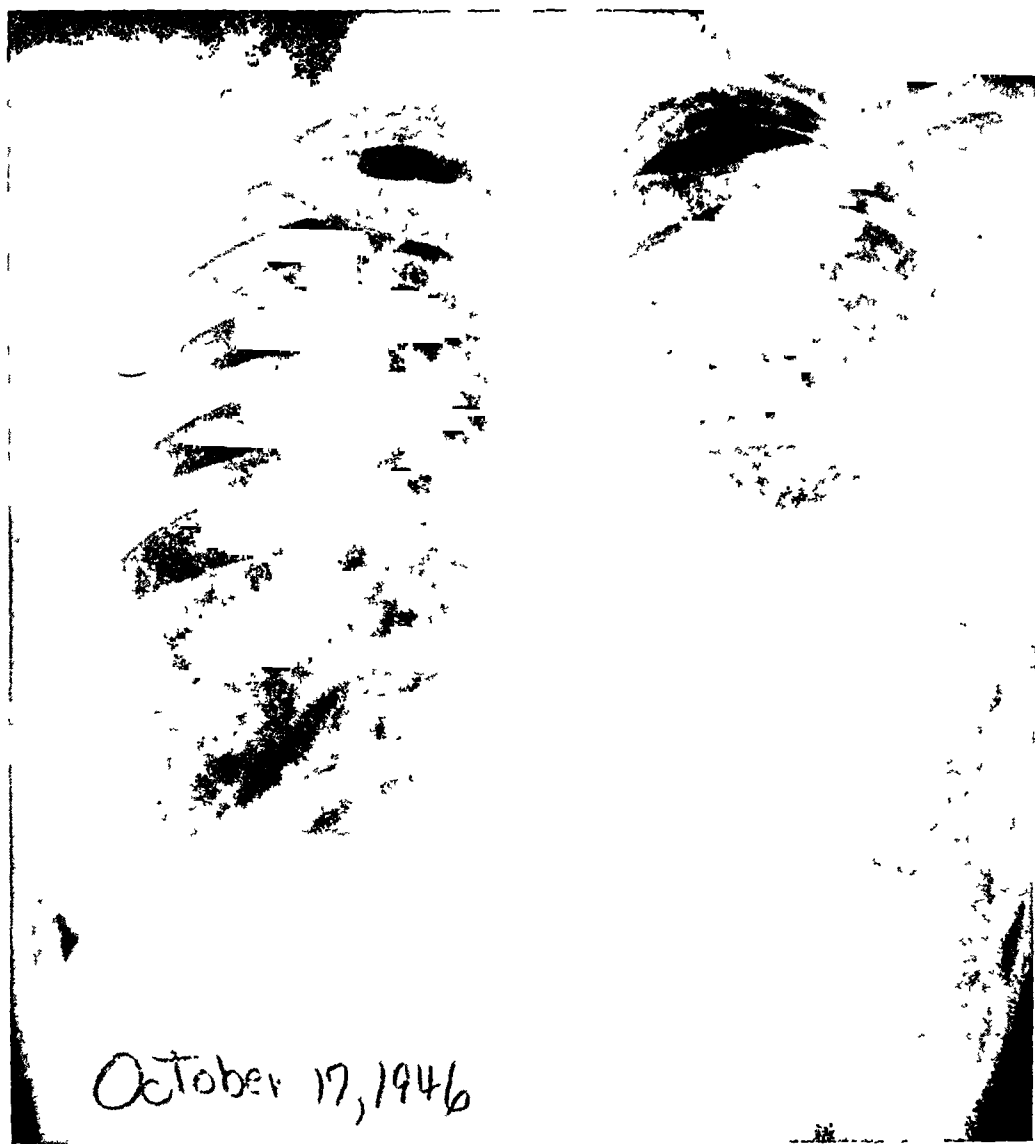


FIG. 2a. Patient P.Be. Forty-two year old white female. Confluent pneumonic infiltration, mostly in pectoral and lingular segments of left upper lobe. Prior roentgen-ray within three months had shown minimal infiltration; greatest part of pneumonic extension known to have occurred within one month. Note cavity at level of third anterior rib.

All such satisfactory immediate results in adults occurred in patients with patchy pneumonic or confluent pneumonic lesions (groups Ia and Ib, table 1),

\* The term *cavity closure* is used to designate instances in which cavities, recognizable on at least two stereo-roentgenographic examinations, were no longer seen in two or more subsequent examinations. The term *sputum conversion* is used to describe instances in which tubercle bacilli, previously demonstrable and usually abundant in the sputum, could no longer be detected on culture or direct examination of concentrated sputum or gastric washings on two or more successive observations.

examples of which are shown in figures 1 and 2. The result in the child with a progressive primary lesion was also satisfactory. No instances of such extensive roentgenologic clearing and cavity closure were observed in the patients with caseo-cavernous lesions (group Id, table 1). Two of the

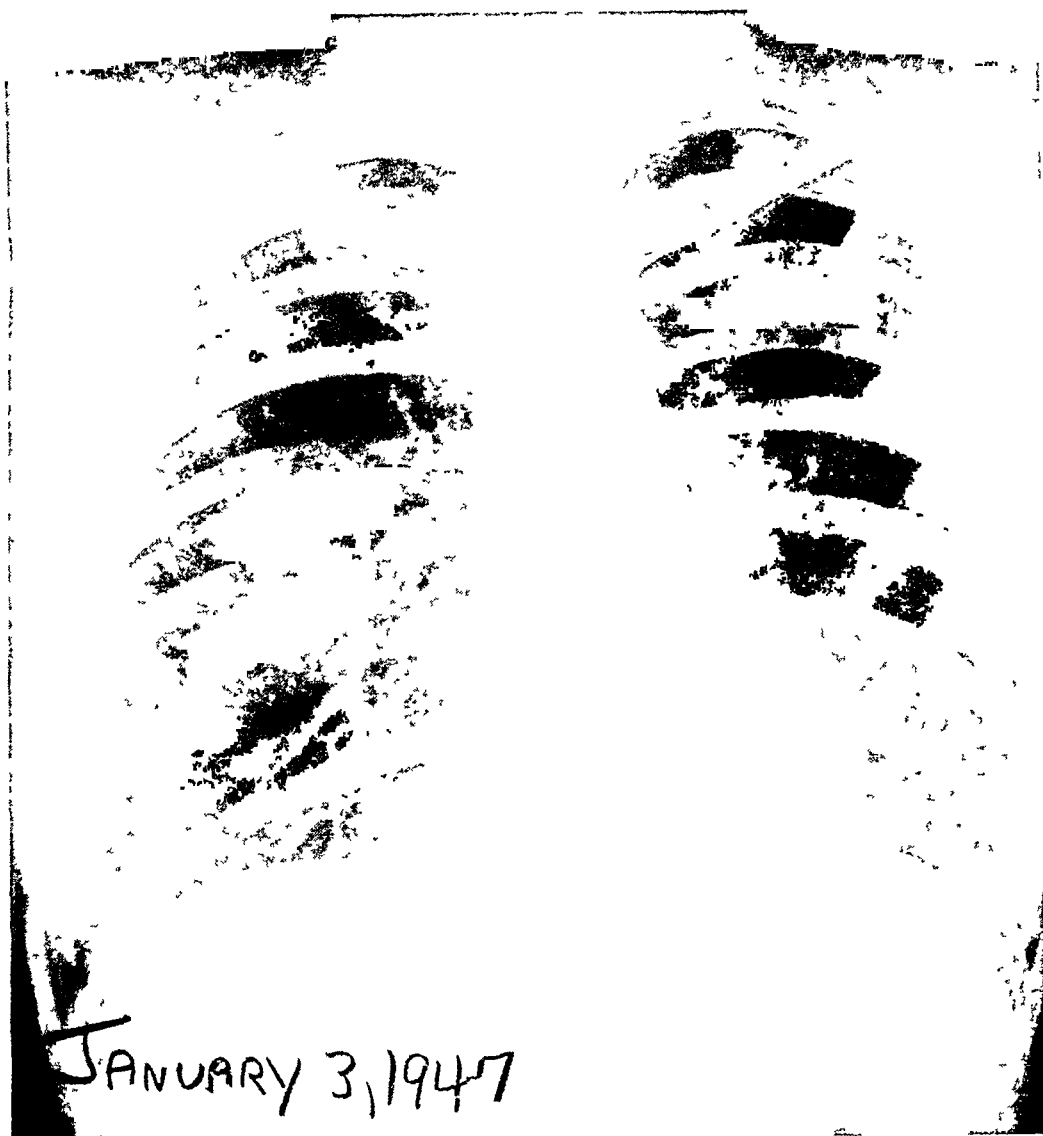


FIG. 2b. Patient P.Be., after streptomycin treatment which was discontinued on sixty-fourth day because of moderately severe skin reaction. Note cavity.

patients who attained satisfactory early remissions\* received treatment for 120 days, two were treated for 63 to 120 days, and in the remaining five (including the one patient who received only 1 gram daily) the total period

\* The term *early remission* is here used to designate the status of patients who were: asymptomatic, afebrile, discharged no tubercle bacilli, had stationary or regressive lesions by roentgenography, and cavity was not present; this condition having persisted for more than one but not necessarily as long as the three months required by official N. T. A. Diagnostic Standards for the designation of *apparently arrested*.

of streptomycin therapy was only 42 days. There was no evidence that either the confluent pneumonic lesions or the cavities in these cases were complicated by the presence of bronchial obstruction. Bronchoscopy was necessarily omitted in the most acute cases because of the danger of spreading the disease, but the physical signs excluded with reasonable certainty the

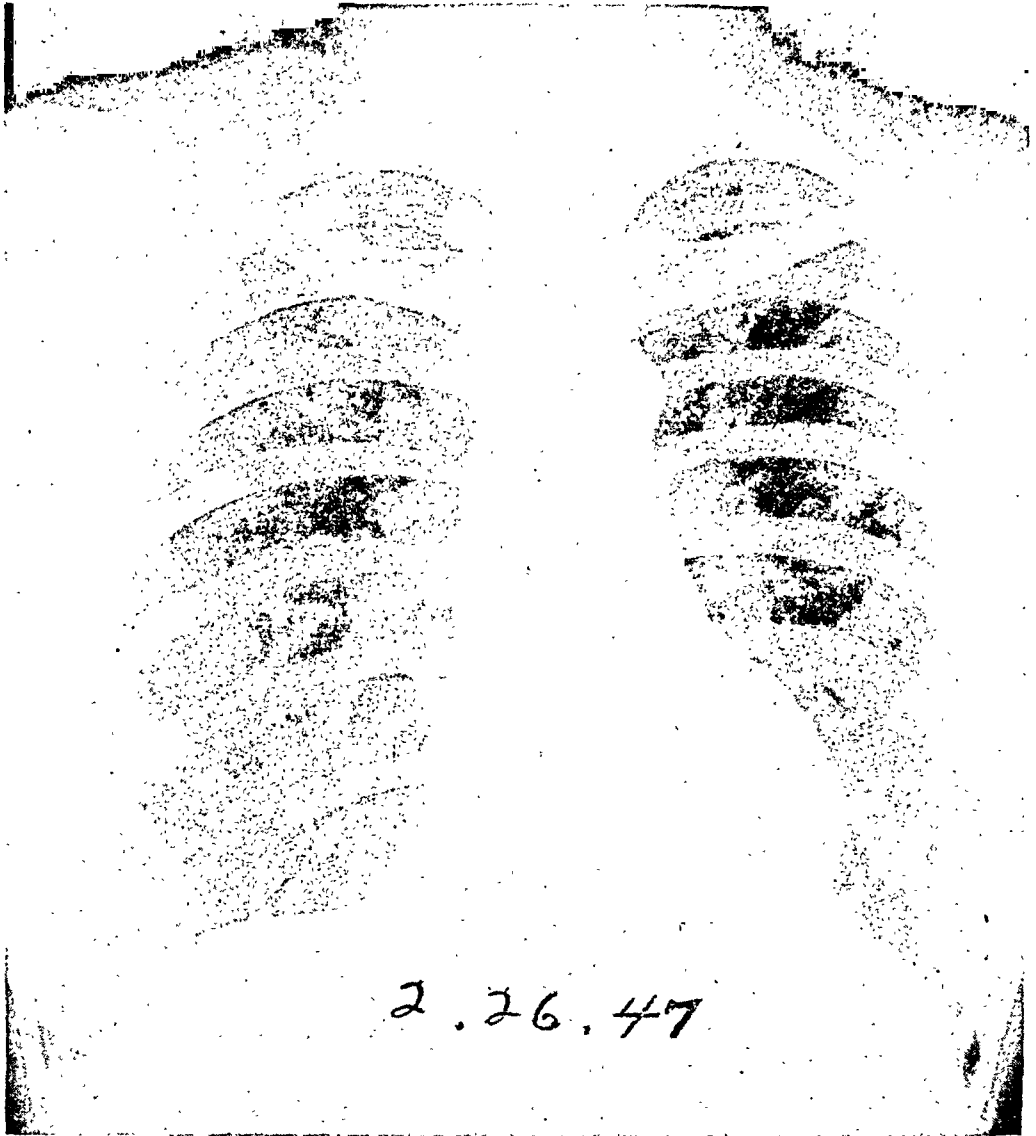


FIG. 2c. Patient P.Be., two months later. Note further improvement with disappearance of cavity although treatment was not resumed. Dose 3.0 gm. daily.

possibility that confluent shadows were caused by atelectasis or "drowned lung" secondary to bronchial obstruction. The halting of the onward progress of the lesion and the onset of roentgenologic clearing occurred uniformly within two to four weeks of the institution of the antimicrobial therapy. The speed with which extensive roentgenologic clearing and

cavity closure were completed in six of the patients equalled or exceeded the most rapid improvement hitherto observed by the present investigators on bed rest alone. In the others, although the onset of improvement appeared early, the greater part of the roentgenologic clearing did not occur until after the first six weeks of the antimicrobial therapy. It is of interest that the clearing which occurred in these latter patients in the second and third

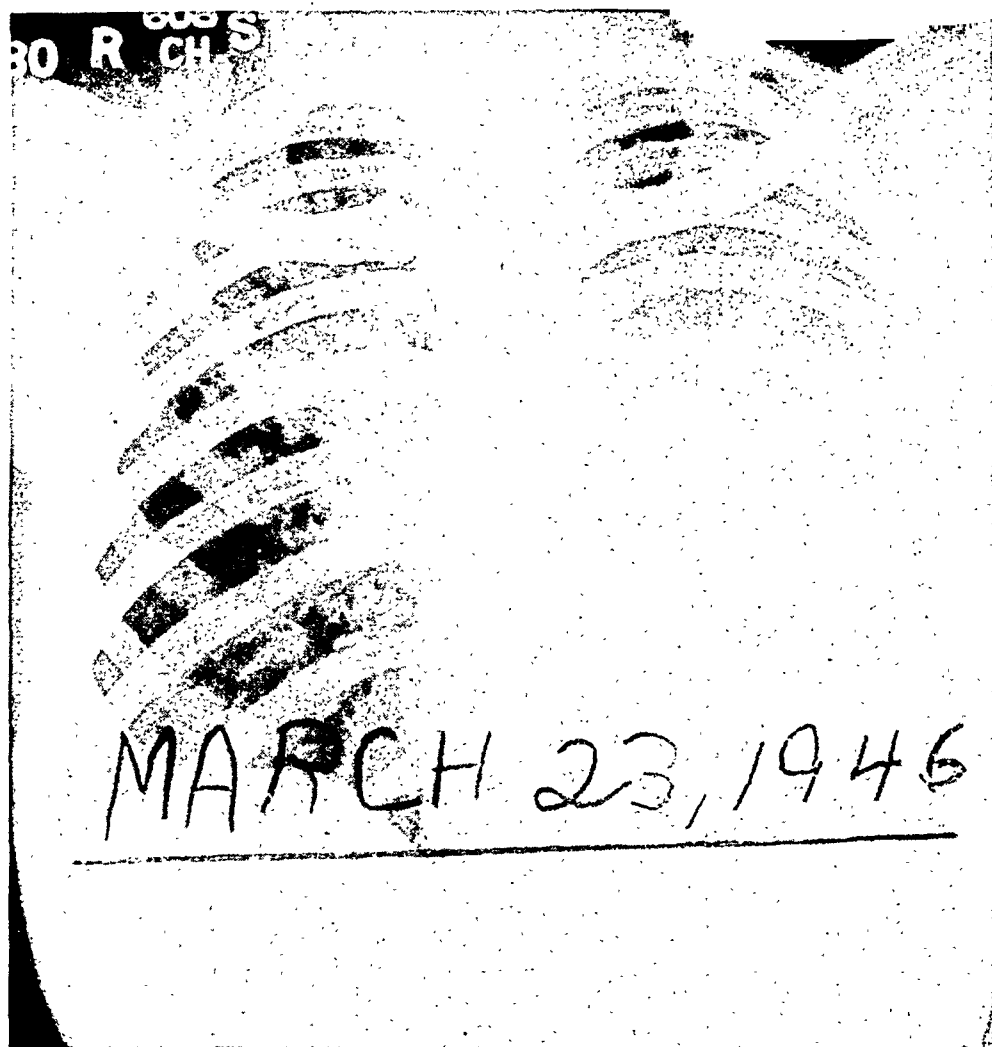


FIG. 3a. Patient B.Ir. Thirty-three year old colored woman. Before streptomycin treatment. Confluent tuberculous pneumonia of left lower lobe with patchy pneumonic infiltration in opposite lung.

months after the start of therapy was equally extensive whether the streptomycin therapy was continued for 120 or for only 42 days.

In general, the clearing of the presumed exudative lesions and the disappearance of the cavities proceeded simultaneously. In several instances, however, extensive resolution preceded cavity closure and the cavities became less prominent as a result of the disappearance of the surrounding zone of

inflammation. The period from the start of antimicrobial therapy to the closure of all cavities (in each individual patient) ranged from three to 12 weeks in these predominantly exudative infections.

The rate of disappearance of tubercle bacilli from the sputum and gastric contents varied according to the speed with which the lesions resolved and



FIG. 3b. Patient B.Ir. 11 months later. Much of the clearing had taken place before end of 120 day course of streptomycin but improvement continued after end of therapy. This patient later relapsed.

cavity closure occurred. In some instances, the first few negative examinations were followed by one or more that were positive, which in turn were followed by several or more negative observations. Recurrence of occasionally positive sputum, with bacilli present in relatively small number, is not uncommon after initial conversion by any method of treatment, and does not in itself indicate eventual therapeutic failure. Using the arbitrarily

determined value of two successive negative smears or cultures, tubercle bacilli "disappeared" from the sputum and gastric washings of these nine patients between the second and the eighth week after the start of streptomycin therapy.

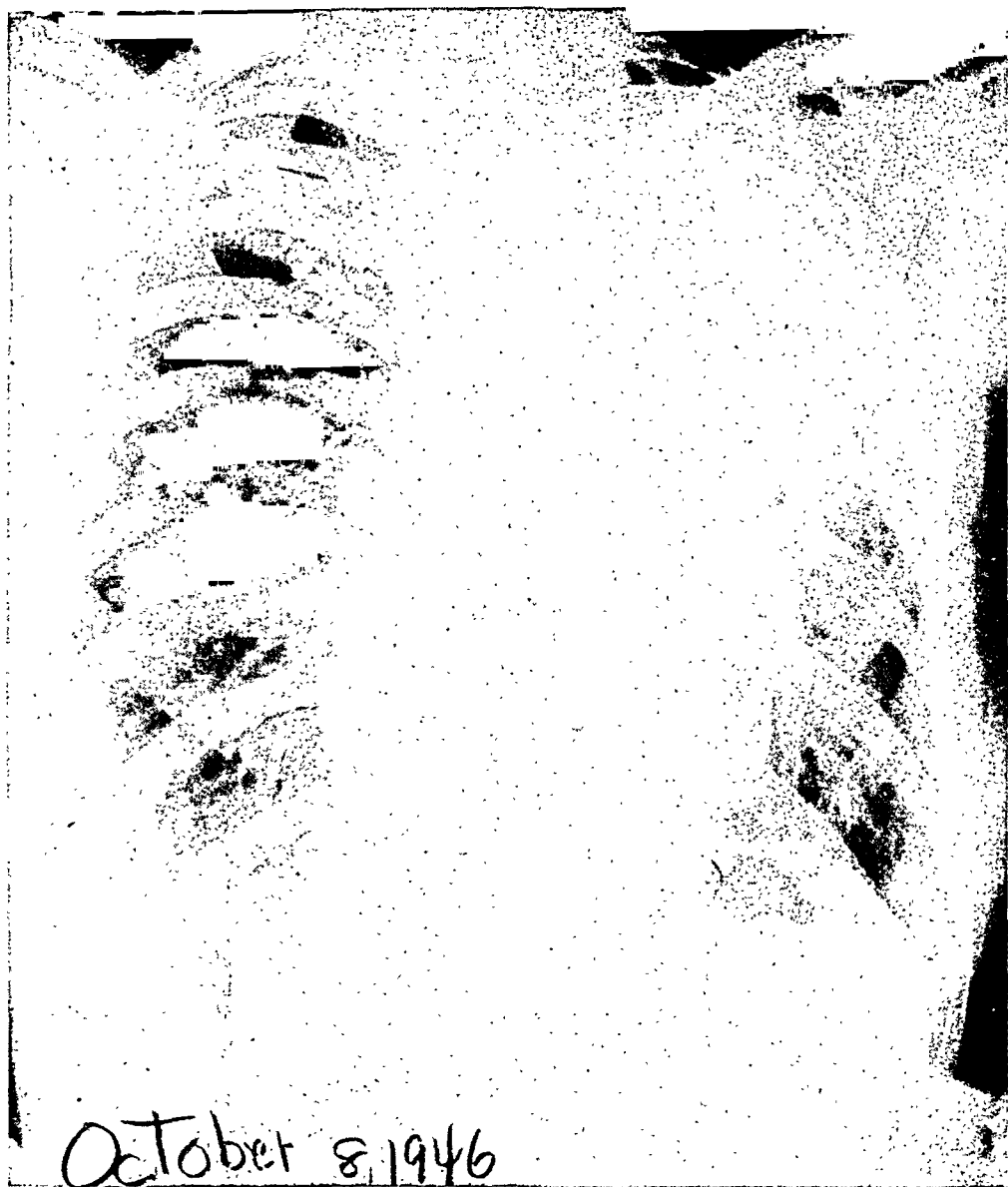


FIG. 4a. Patient G.Wi. Thirty-nine year old colored woman. Confluent pneumonic involvement of left upper lobe of approximately two months' duration. Bucky film of this date (not shown) revealed considerable excavation in infraclavicular region. Temperature ranging above  $39^{\circ}$  C.

All of the patients were confined to bed for approximately five months after cavity closure. This measure was adopted both because of the potential seriousness of the lesions before treatment and the lack of knowledge concerning the stability of drug-induced remissions. The remissions have been

maintained for more than six months in four patients who might therefore be classified as *arrested*, except that the criteria regarding physical exercise have not been fulfilled.

*Relapse:* Clinical, roentgenologic and bacteriologic evidence of relapse appeared within 10 months of the completion of therapy in three of the nine

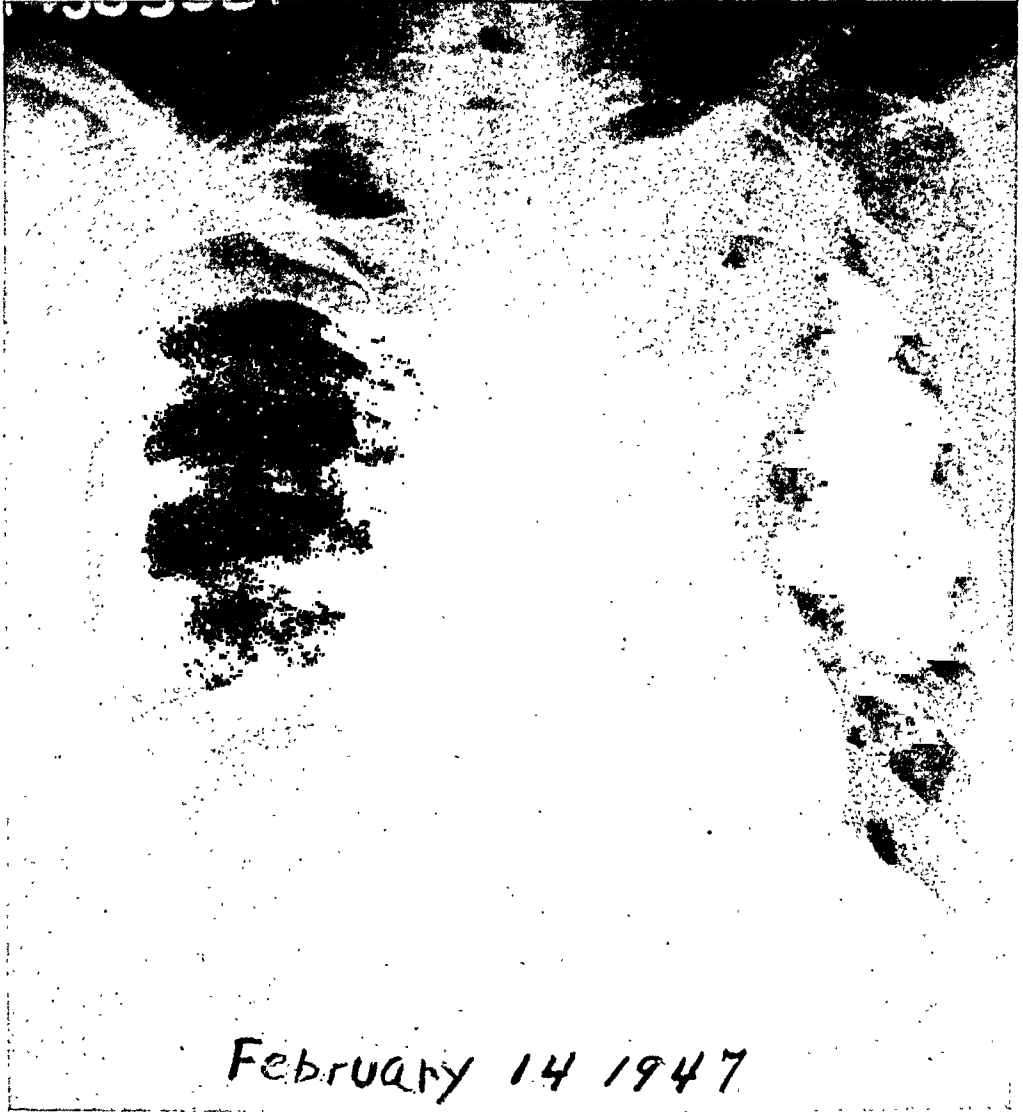


FIG. 4b. Patient G.Wi., after 120 day course of streptomycin. Note extensive regression but persistence of dense infiltration in apical region with irregular cavities.

patients who had attained early remissions. Two of the relapses appeared between the first and third months after streptomycin therapy had been discontinued. As both of these occurred despite the continuation of a regimen of bed rest, they must be considered as therapeutic failures. They have subsequently received collapse therapy. The third patient was a 33 year old colored woman (figure 3), in whom reactivation of the disease oc-

curred under circumstances of grossly inadequate rest and nutrition, 10 months after the cessation of streptomycin. Antimicrobial therapy was not reinstituted in any of these patients who relapsed after control of the infection had apparently been attained.

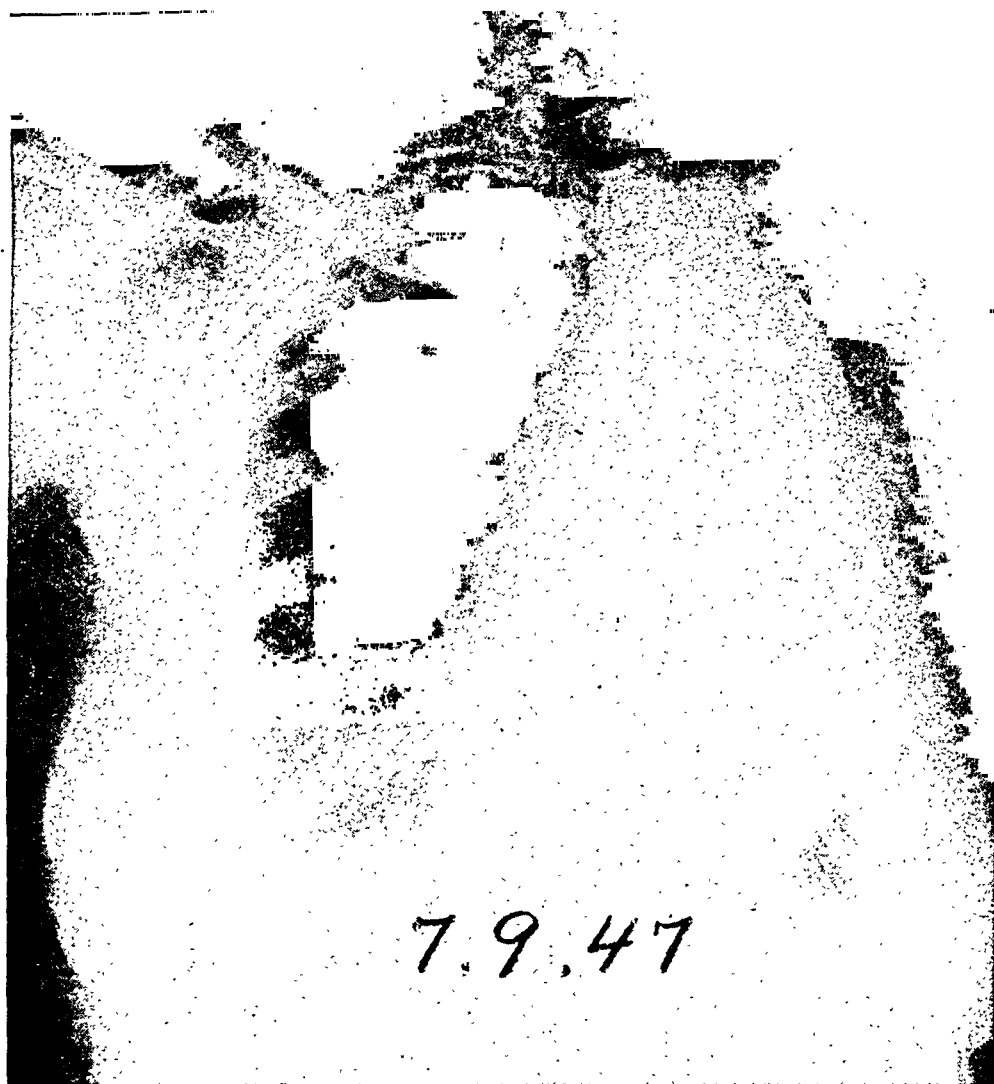


FIG. 4c. Patient G.Wi., after thoracoplasty operation. The pleural thickening on the right is result of pleurisy with effusion  $3\frac{1}{2}$  years earlier.

*Continued Quiescence without Cavity Closure.* In six of the 18 patients in the group with predominantly exudative lesions there was a variable degree of roentgenologic clearing and cavity shrinkage which did not continue to the point of complete closure. Although the change in the status of the disease when therapy was discontinued was not as favorable in these as in the patients who attained satisfactory early remissions, the total improvement was usually impressive. In all instances, the disease had been



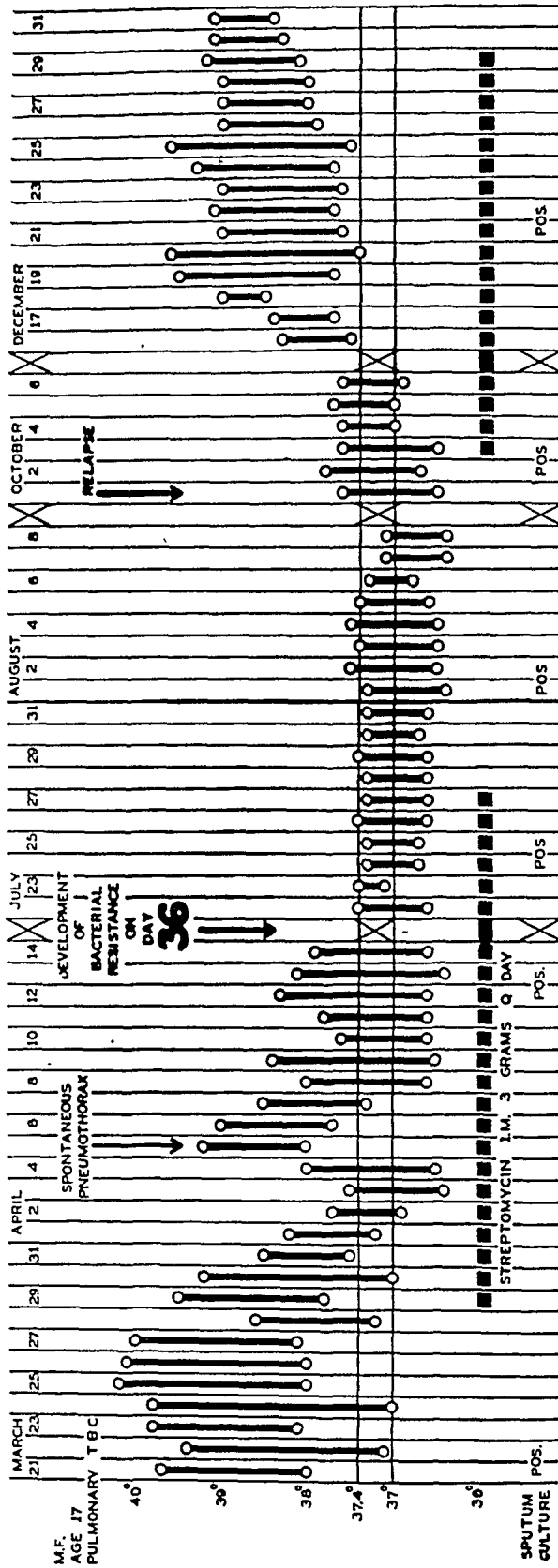


FIG. 5a. Patient M.F.I. Seventeen year old colored boy with casco-cavernous disease of at least 10 weeks' duration. Temperature chart.

actively progressing before the streptomycin treatment and for various reasons collapse therapy had been considered inadvisable. Three received collapse therapy subsequent to the streptomycin. In all three the collapse therapy (pneumothorax 1, thoracoplasty 2) has been initially successful

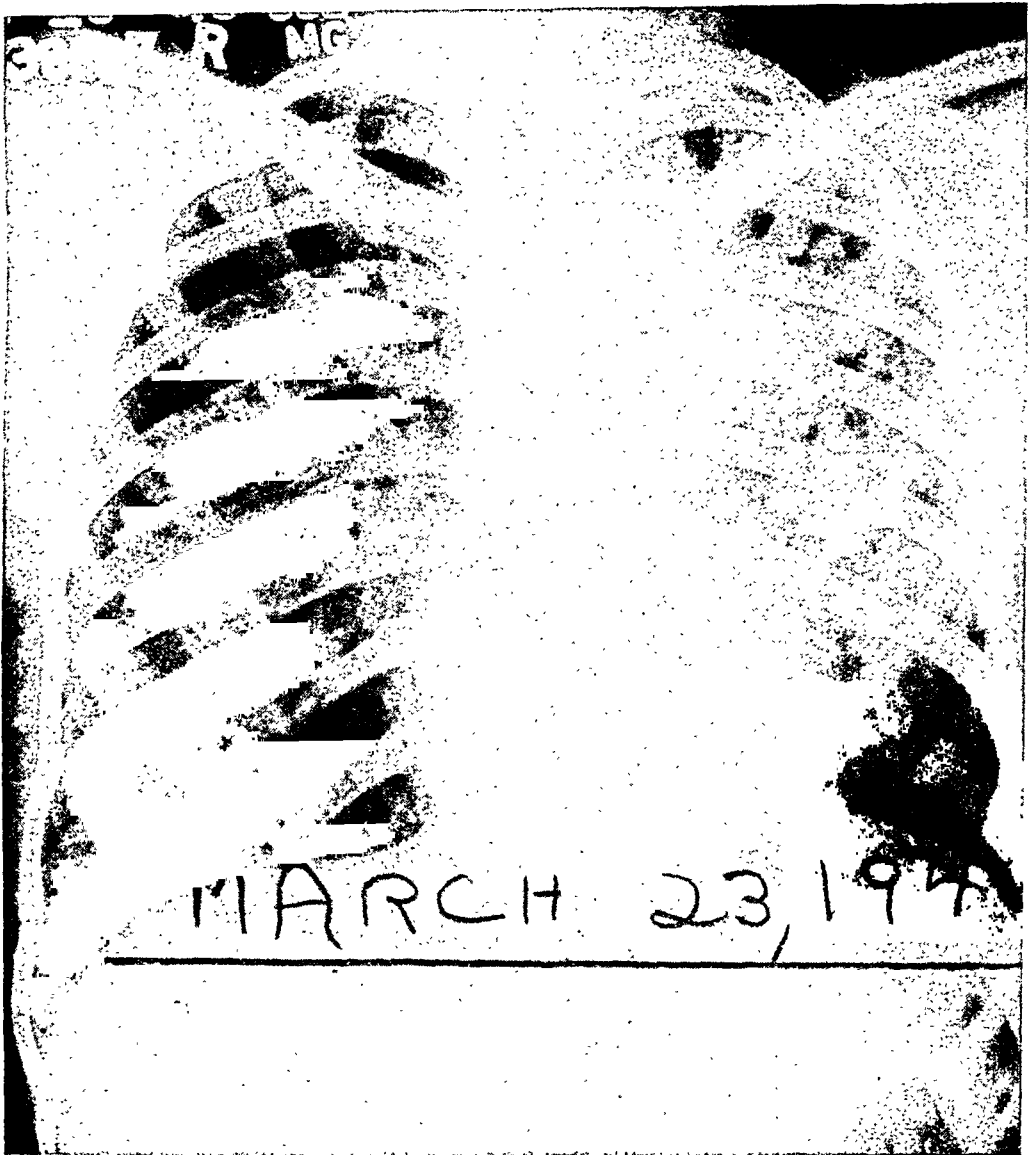


FIG. 5b. Patient M.F.I., roentgen-ray before treatment. Note multilocular cavities occupying almost entire apical region and punched out smaller cavities below.

with prompt cavity closure and sputum conversion. This is of particular interest because the disease prior to streptomycin had in each instance been considered too acute to justify the use of such procedures. A representative example is illustrated in figure 4.

*Improvement, Chiefly Symptomatic, Followed by Further Excavation and Resumption of Progressive Course.* In three of the total group of 18

patients with predominantly exudative lesions, the course under streptomycin therapy consisted of an initial period of clinical improvement, followed by further excavation of the diseased area of variable extent, and eventual resumption of steadily progressive tuberculosis. All of the three patients had large or multilocular cavities within confluent pneumonic segments.



FIG. 5c. Patient M.Fl., five weeks after end of 120 day course of streptomycin. The apparent contraction of the extensively involved left lung may be due in part to the therapy but can also be attributed to an intercurrent spontaneous pneumothorax. Spread of an originally small focus in the opposite lung is now apparent.

which had apparently progressed to the stage of massive caseation (group Id, table 1).

A representative example of this type of case may be seen in figure 5. The patient was a 17 year old colored boy who had been acutely ill with a confluent tuberculous pneumonia for 10 weeks before streptomycin therapy was started. An abrupt defervescence occurred within 72 hours of the

institution of antimicrobial therapy. Several days later, however, the temperature again rose in association with a spontaneous pneumothorax. Despite the acute nature of the underlying process, only a small sterile pleural effusion accumulated. The temperature promptly fell to normal as the air and fluid resorbed and the hydropneumothorax space became obliterated.

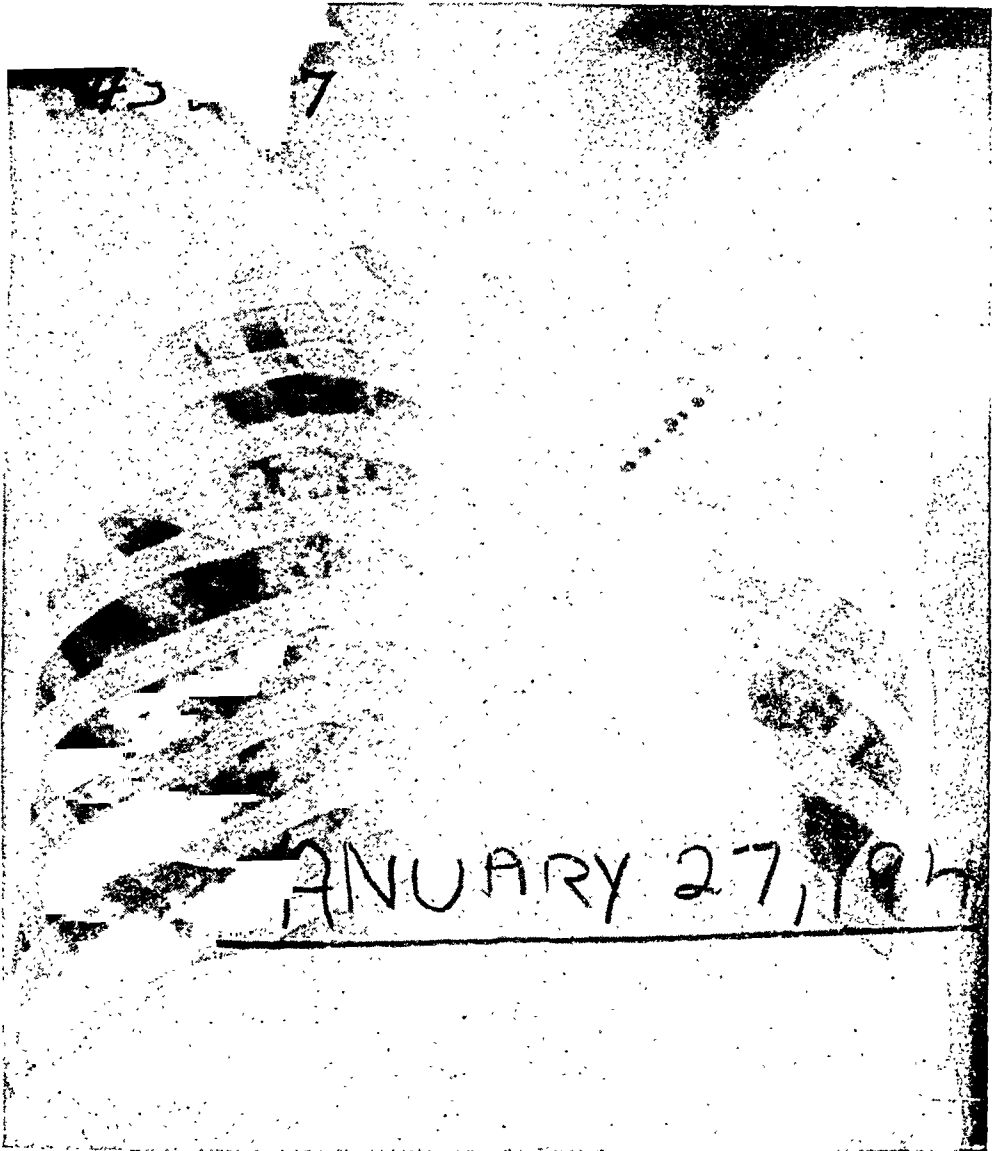


FIG. 5d. Patient M.FI., further progression despite resumption of streptomycin after bacterial resistance had been observed in vitro.

Throughout the ensuing three months of streptomycin therapy, the initial symptomatic improvement was maintained. There was no roentgenologic evidence that new areas of lung were becoming involved, but no significant objective improvement was evident. All cultures of tubercle bacilli isolated subsequent to the thirty-fifth day of therapy were highly resistant to

the action of streptomycin in vitro. Five weeks after the completion of the first course of drug therapy, reactivation of a tiny area of disease in the contralateral lung was evident by roentgenography. Although streptomycin therapy was promptly re-instituted, the infection assumed a rapidly progressive course which terminated fatally five months after the first appearance of relapse.

A similar course was observed in the second patient in this group who also has died. The third patient, though still living at the present writing, is given a hopeless prognosis and is virtually moribund. In all three, strains of tubercle bacilli highly resistant to streptomycin in vitro appeared during therapy.

*Summary of the Results in the Group with Recent Predominantly Exudative Pulmonary Tuberculosis with Early Cavitation.* Eighteen patients with various forms of early predominantly exudative tuberculosis received streptomycin for periods ranging between 42 and 120 days. Satisfactory early remissions were attained by nine of the group. All of the nine had patchy or confluent pneumonic lesions which, although extensive, had apparently not caseated massively or excavated large segments of lung substance. In two instances, the early remission was followed by relapse within two months of the completion of streptomycin therapy. In six patients, the institution of streptomycin therapy was followed by an impressive degree of improvement which fell short of full remission. In three patients whose disease had presumably progressed to extensive caseation, a short period of improvement was followed by the resumption of a rapidly progressive course.

In the total of 18, there are seven whose disease was apparently controlled for six months or longer without the aid of collapse therapy. An additional five have had collapse therapy which in every instance has been apparently successful, although the patients would all have been regarded as unfavorable risks prior to the improvement under streptomycin.

*Group II. Chronic Pulmonary Tuberculosis with Fibro-Cavernous Secondary Changes.* In contrast to the response of the early predominantly exudative cases, the improvement was relatively small in the group of patients with disease of more chronic type which was either known to be of relatively long duration or showed roentgenographic evidence of established and extensive fibrosis. In most, exudative lesions were present also but this component was relatively small or associated with extensive involvement of chronic character. The results are shown in table 1, group II.

Of the 18 patients in this group, 16 received the 3.0 gram daily dose and two received the 1.0 gram dose. The symptomatic response, as might be expected, was seldom impressive and never dramatic. Likewise, the character of the signs elicited on examination of the lungs was not so strikingly altered, although the number of râles usually diminished appreciably during the streptomycin treatment. In all but one of the 18 patients, however, the introduction of streptomycin therapy was followed by roentgenologically demonstrable regression of some of the infiltrative process. There was

usually also a definite reduction in cavity size. In several instances in which persistence of cavitation was associated with endobronchial disease, a rapid

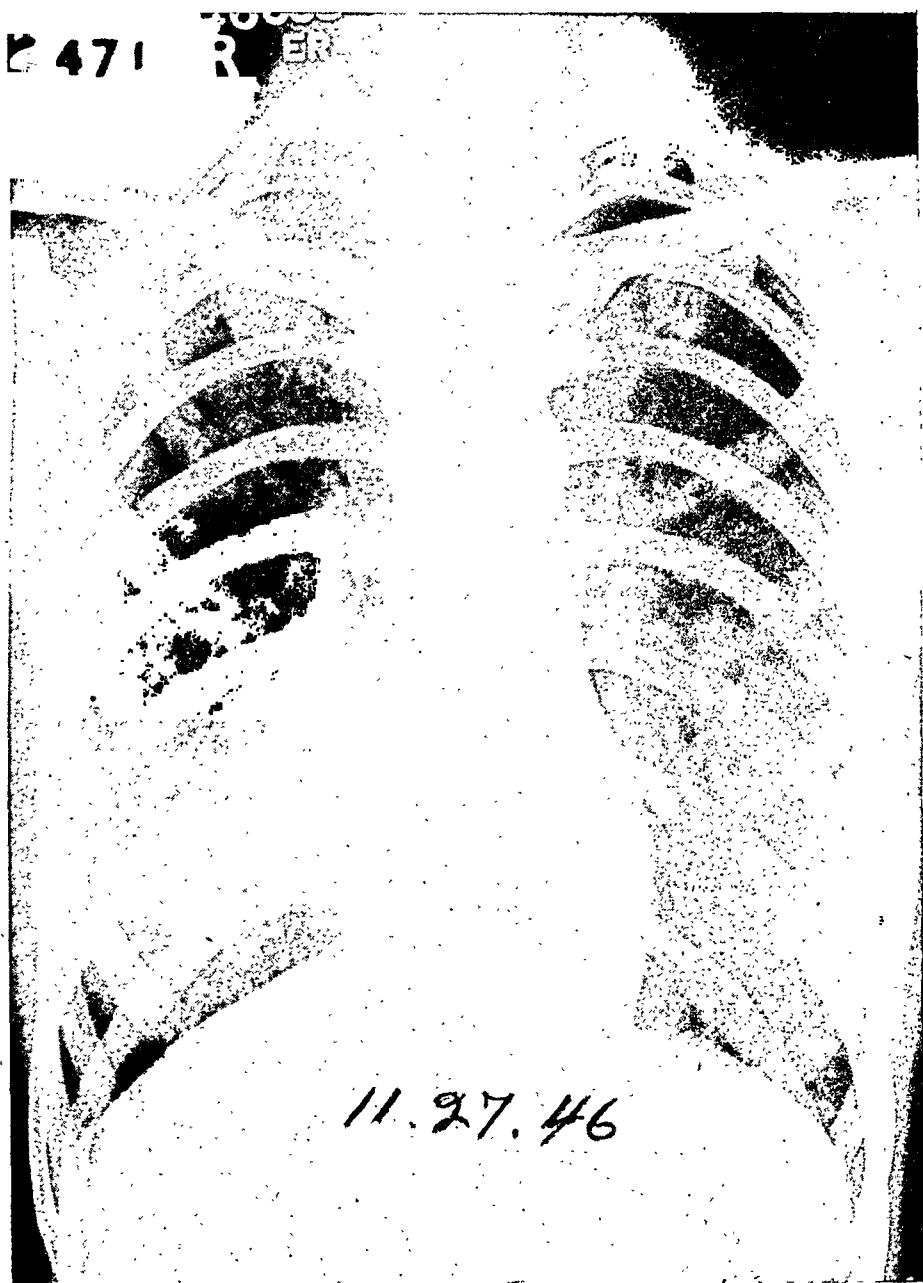


FIG. 6a. Patient C.McC. Before streptomycin treatment. A 19-year old white woman with extensive involvement of right lung of unknown duration. A febrile episode two months before was possibly related to spread of the disease. At start of therapy had been afebrile for seven weeks. No clearly defined cavitation.

shrinkage of the cavity occurred, presumably as a consequence of regression of the bronchial lesion.

Satisfactory early remissions were observed in only four patients, of whom three attained both cavity closure and sputum conversion. The

fourth had no cavity clearly discernible to begin with. This patient is of particular interest because the clearing, which was ultimately very satisfactory, did not begin to take place appreciably until after treatment had been

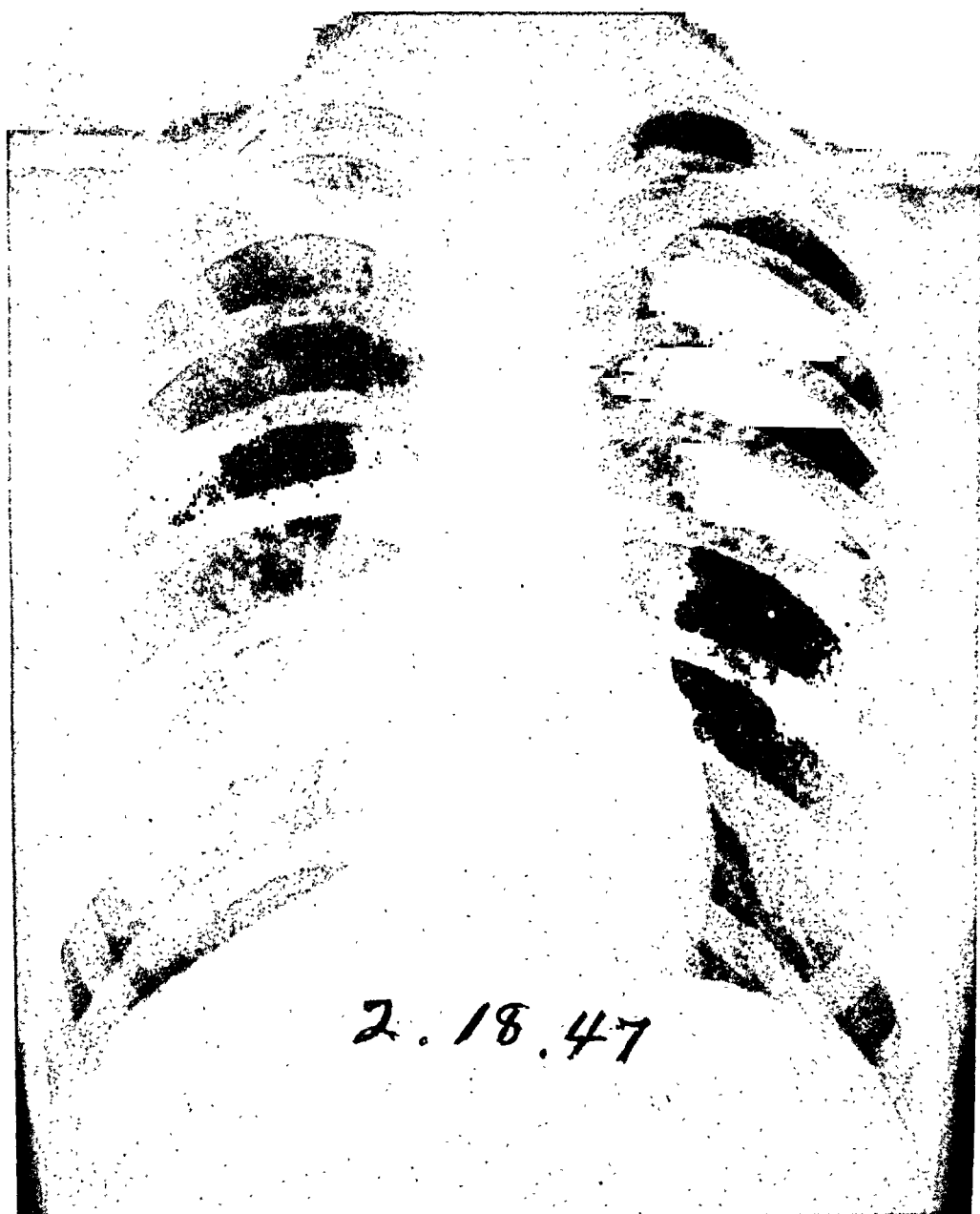


FIG. 6b. Patient C.McC., on seventy-fourth day of 90 day course of treatment. Note lack of any appreciable change at this time.

concluded, yet after regression had started it proceeded with considerable rapidity (figure 6). A fifth patient (table 1, group II) became sputum negative but there was persistence of an obvious cavity. This patient was one among four who were subjected to thoracoplasty. Apparent cavity

closure was accomplished in each, but sputum conversion followed in only two of the four. It is noteworthy that in these, as in the patients in the more acute group previously described, thoracoplasty had been considered

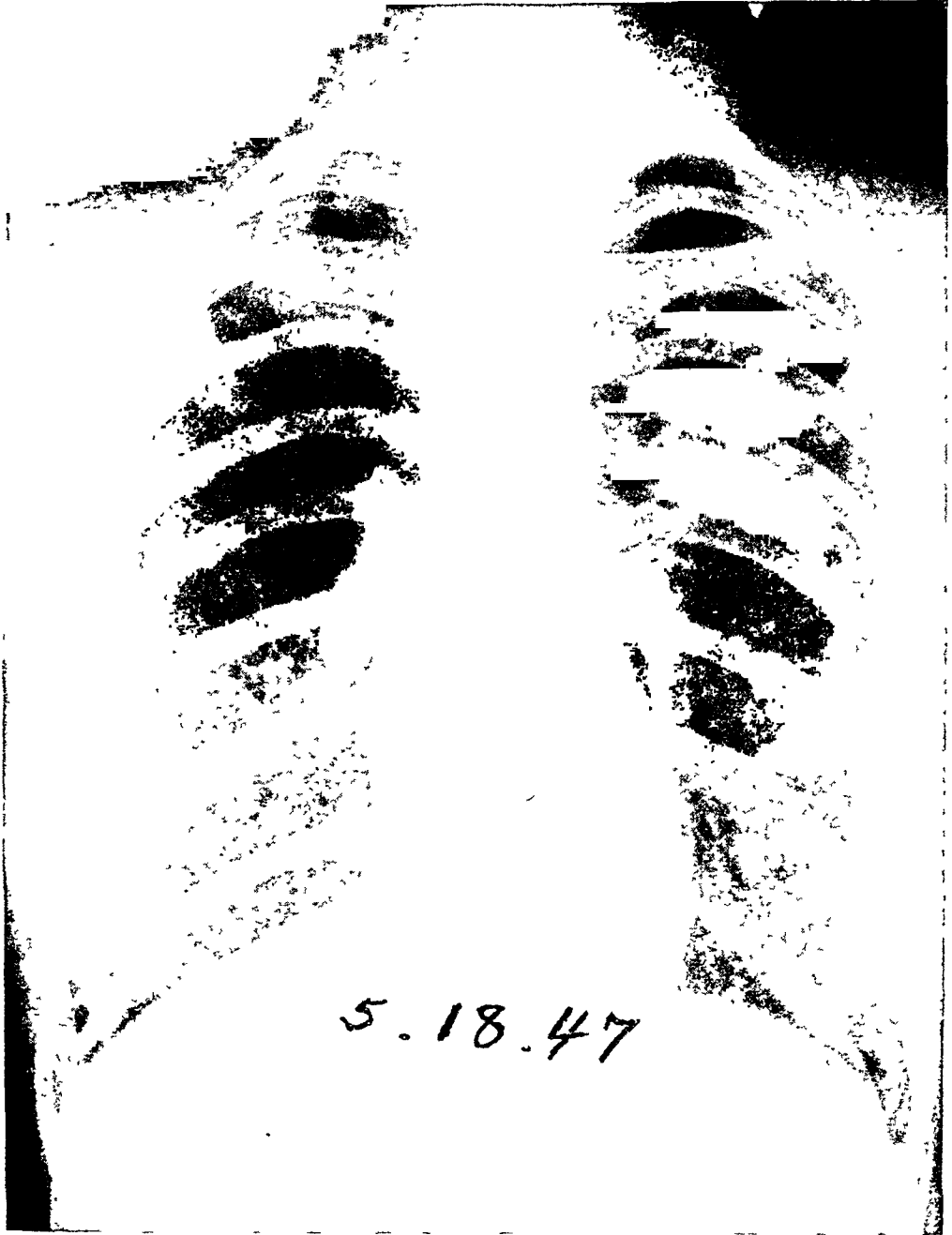


FIG. 6c. Patient C.McC., two and one-half months after end of streptomycin therapy, showing considerable "delayed resolution."

inadvisable prior to streptomycin because of actively advancing lesions in one or both lungs. Two did not appear as if they would ever be suitable candidates for the operation and in the other two the operation could



scarcely have been considered feasible within six months with the best fortune under standard treatment. The improvement during streptomycin treatment was sufficient to make operation appear feasible within eight to 12 weeks and it was accomplished in all without untoward developments, such as post-operative spread. The first stage operation was not performed in

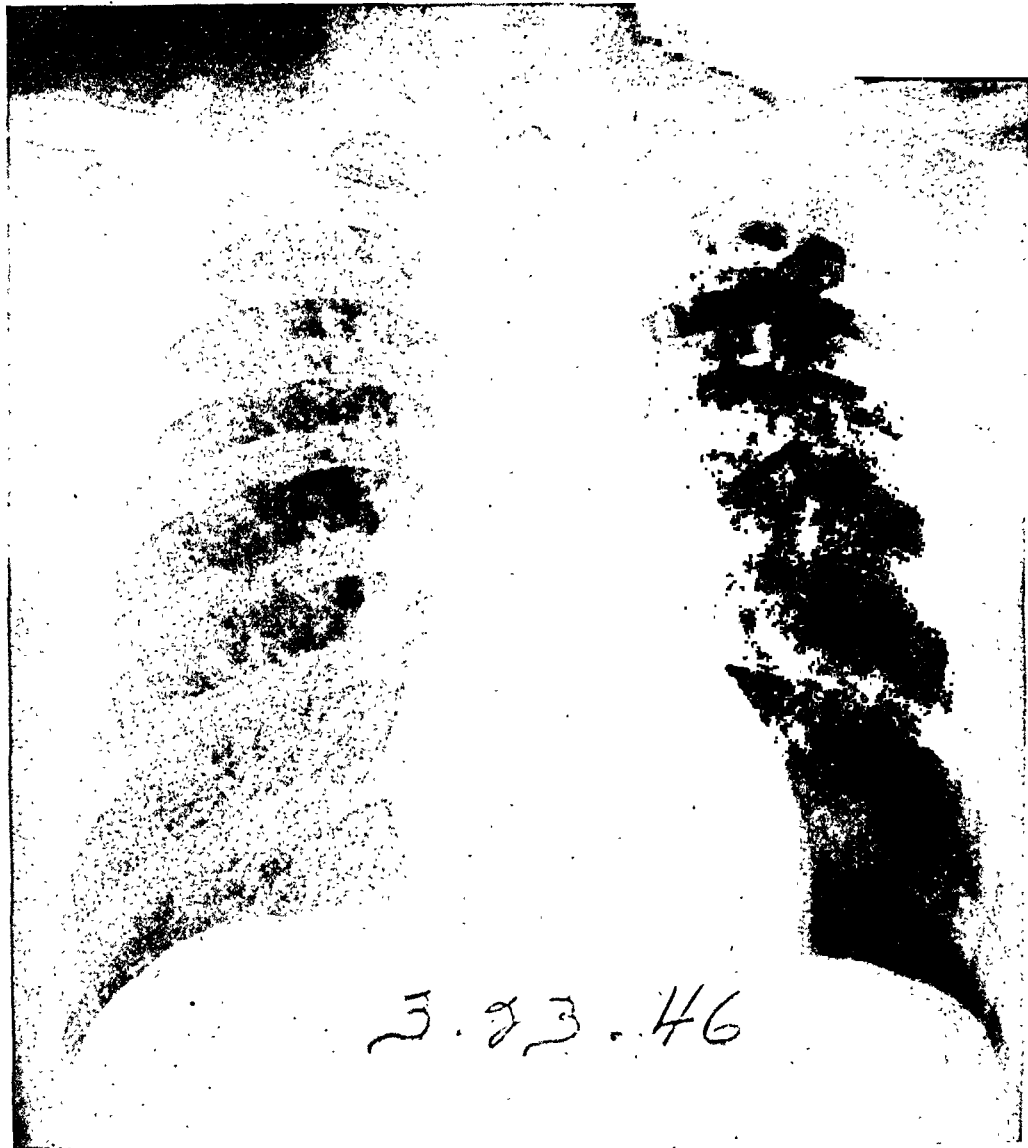


FIG. 7a. Patient J.Sa. A 53 year old white man with chronic fibro-cavernous involvement of both lungs. Before streptomycin treatment.

any instance until it appeared that the maximum regression and cavity shrinkage which was to be anticipated had occurred.

In the remaining 10 of the 18 patients with chronic fibro-cavernous lesions, a period of symptomatic and minor roentgenologic improvement observed during the early weeks of streptomycin therapy was followed by a

return to the pre-treatment state or an actual extension of the process. The loss of the apparent gain under antimicrobial therapy was preceded, in every instance, by the appearance of strains of tubercle bacilli which were highly resistant to streptomycin *in vitro*. In addition, and presumably unrelated to the drug-resistance, certain of these cases became complicated by such incidents as profuse hemorrhage or spontaneous rupture of the lung.

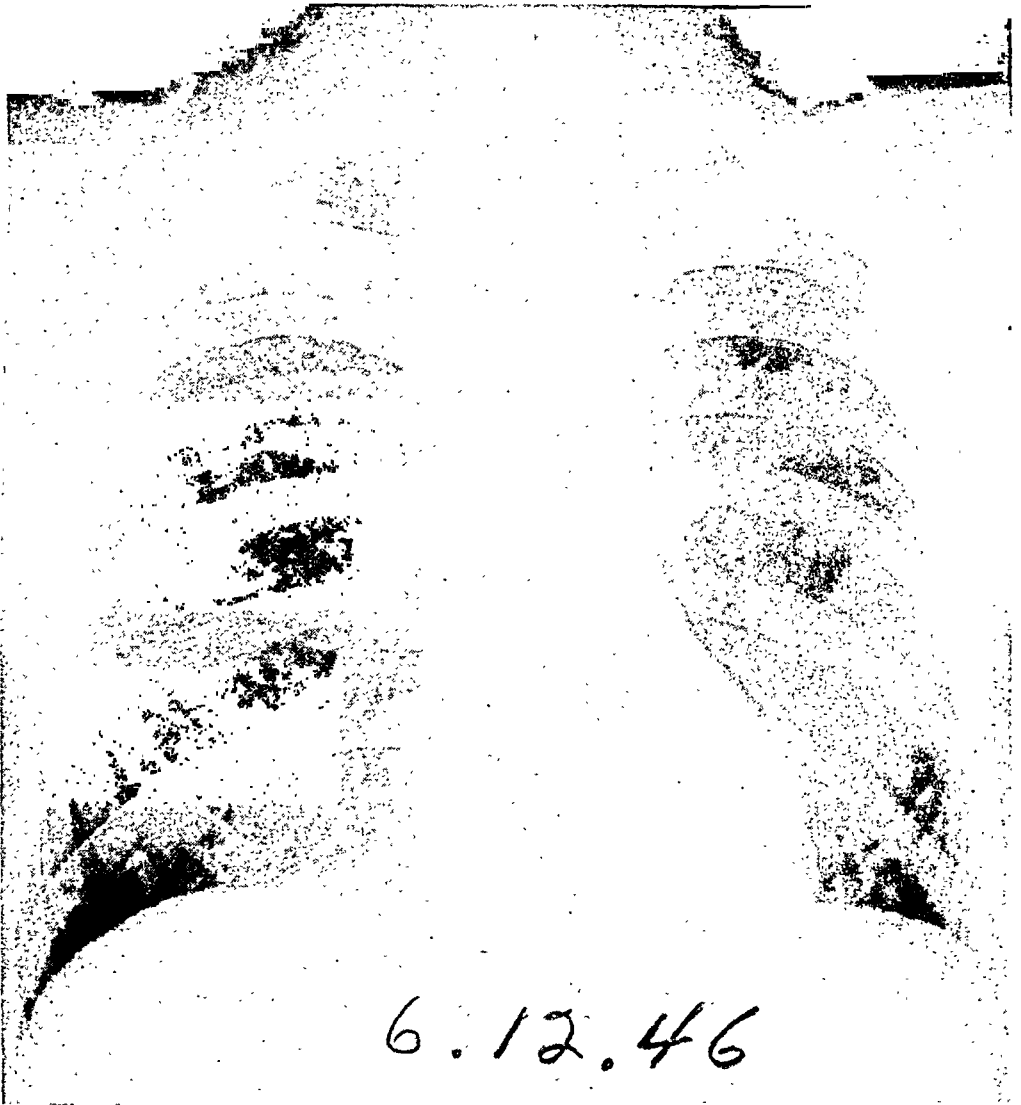


FIG. 7b. Patient J.Sa., early in third month of treatment. Note contraction of cavities.

A representative example of the type of therapeutic failure observed in chronic fibro-cavernous tuberculosis may be seen in figure 7.

The patient was a 52 year old man with bilateral chronic predominantly proliferative tuberculosis with three cavities, ranging from 2 to 4 cm. in diameter. During a four month period of observation on bed rest before streptomycin therapy, there had been essentially no change in the extent

of involvement or the size of the cavities. The patient had only mild toxic symptoms with low grade fever. In the first 30 days of antimicrobial therapy, the fever disappeared and there was roentgenologic evidence of slight regression of the bilateral infiltrations with a definite reduction in the size of all three cavities. On the sixty-eighth day of streptomycin therapy, tubercle bacilli isolated from the sputum were highly resistant to streptomycin in vitro as were all cultures obtained subsequently. Although this development was not immediately followed by any change in the condition of the patient, on the seventy-third day of drug therapy the left lung spontaneously ruptured. A tuberculous empyema developed which was

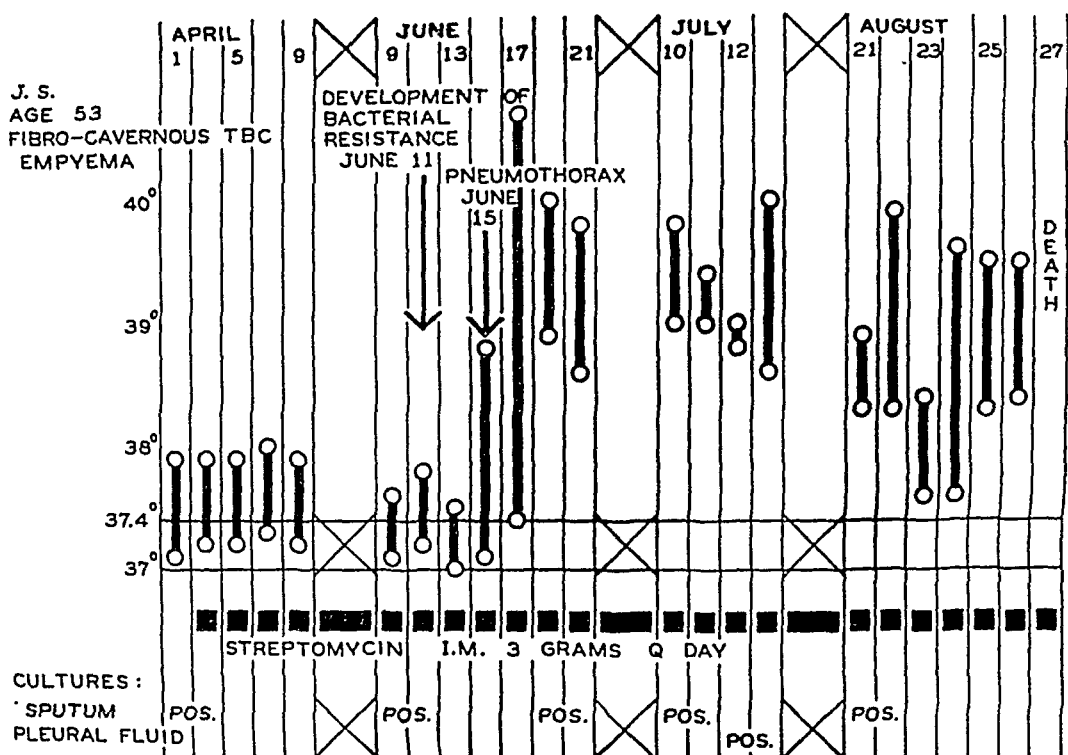


FIG. 7c. Patient J.Sa., temperature chart. Spontaneous pneumothorax occurred after development of bacterial resistance (see text).

unsuccessfully treated by repeated aspirations and instillations of streptomycin in 1 per cent solution. Although open surgical drainage was instituted and maintained and the antimicrobial therapy continued, the infection (with drug-resistant tubercle bacilli) assumed an acute febrile course which terminated fatally on the one hundred thirty-sixth day of streptomycin therapy.

In summary, of 18 patients with predominantly fibro-cavernous pulmonary tuberculosis, three attained cavity closure and sputum conversion during streptomycin therapy. A satisfactory result was observed in a fourth patient who had no definite cavitation to begin with and who attained sputum conversion with extensive regression of infiltration. Four patients, who

had previously been considered poor risks for thoracoplasty were sufficiently improved so that operation was performed without untoward complications. In the remaining 10 patients there was a variable degree of temporary improvement followed by resumption of progressive tendencies. None of these were suitable cases for collapse therapy after the failure of streptomycin to promote satisfactory remission had become apparent. In several instances collapse therapy might have been feasible had it been undertaken at the time of maximal improvement, before the disease reëntered an advancing phase.

*Laryngeal and Tracheobronchial Lesions.* Ulcerative lesions of the larynx or bronchi were present before streptomycin therapy in eight of the total group of 43 patients with pulmonary tuberculosis. Evidence of healing appeared in all of these lesions within one week of the start of therapy and the process was usually completed by the end of the second month. In one patient, a bronchial lesion subsequently recurred under streptomycin therapy at a time when the bacilli obtained from the sputum were streptomycin resistant in vitro. Lesions remained healed despite the development of drug-resistant bacilli, however, in two patients.

*In Vitro Streptomycin Resistance of Organisms Isolated from Patients with Pulmonary Tuberculosis.* The results of the in vitro determinations of streptomycin sensitivity of the organisms isolated from the patients with pulmonary tuberculosis were similar to the results previously reported for the group with generalized hematogenous infections.<sup>1</sup> Tubercle bacilli could be cultured regularly from 23 of 39 patients during and subsequent to streptomycin therapy. Most of the 16 patients from whom organisms were not obtainable during therapy represented instances in which cavity closure had also taken place.

There was a striking correlation between the appearance of in vitro streptomycin resistance and the duration of therapy. In 11 of the 23 patients who discharged bacilli regularly throughout therapy, the streptomycin was administered continuously for total periods of 75 to 120 days. In all but one of these infections, streptomycin-resistant\* strains of tubercle bacilli appeared during the period of therapy and were isolated regularly thereafter. The exception was a patient from whom drug-resistant bacilli were not obtained until 51 days after the start of a second course of therapy or 244 days after the original institution of streptomycin. When these data are combined with the previously reported determinations on bacilli from the pulmonary lesions of miliary infections,<sup>1</sup> it may be seen that drug-resistant organisms were obtained from all but one of the 17 patients who continued to discharge bacilli throughout a period of therapy of 75 to 120 days.

In contrast to these findings, the appearance of drug-resistant strains of bacilli was observed in only one of the 11 patients who received only 42 days of therapy and who continued to discharge organisms throughout treat-

\* To simplify the discussion the term "streptomycin-resistant" is used to designate strains of tubercle bacilli which are not inhibited by streptomycin concentrations of 500 micrograms per c.c.

ment. In seven of this group the organisms were tested at approximately 100 days after the start of treatment. Organisms from the remaining four infections were drug-sensitive at the completion of therapy but have not been tested thereafter. Seven of the 42 day cases received 3.0 grams of streptomycin daily and in the other four patients the total daily dose was only one gram. The one patient from whom drug-resistant organisms were obtained was on the 3.0 gram regimen.

Streptomycin-resistant strains of tubercle bacilli were observed as early as the second month of therapy in two of the pulmonary infections. In

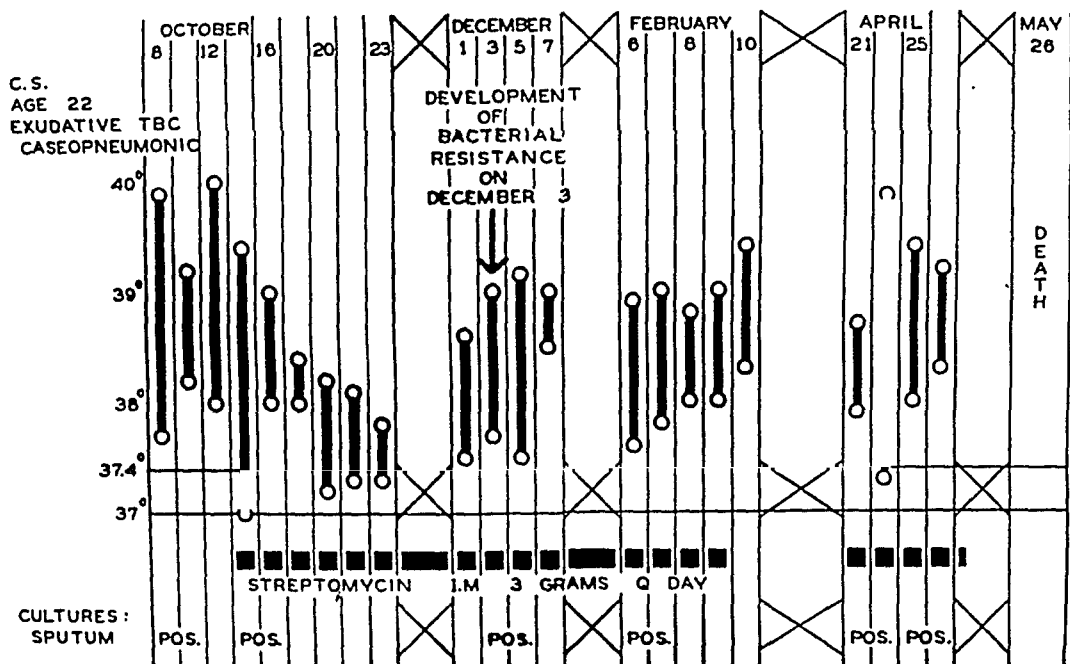


FIG. 8a. Patient C.St. Twenty-two year old colored woman. Temperature course showing early return of fever after initial response to streptomycin.

general, however, in the pulmonary infections as in the generalized hematogenous infections, the majority of the drug-resistant strains appeared in the third month of the streptomycin treatment. The disappearance of the phenomenon of in vitro drug-resistance was not observed. In one patient organisms which were resistant to streptomycin concentrations of 10 micrograms per c.c. but were sensitive to 15 micrograms per c.c. were isolated eight months after completion of the 120 day regimen. This patient had attained cavity closure during therapy so that no organisms had been obtained by culture after the first 31 days of treatment. In all four individuals from whom bacilli could be obtained regularly during the year after the start of drug therapy, the organisms were not inhibited by streptomycin concentrations of 500 micrograms per c.c.

*Correlation between in Vitro and in Vivo Streptomycin Sensitivity.* An apparent correlation existed between the course of a pulmonary infection during chemotherapy and the sensitivity of the bacilli to streptomycin in

vitro. In four of the 11 pulmonary infections from which drug-resistant bacilli were obtained, the discharge of organisms ceased soon after the first demonstration of the phenomenon. These were all instances in which the finding of resistant bacilli represented the last positive culture obtainable

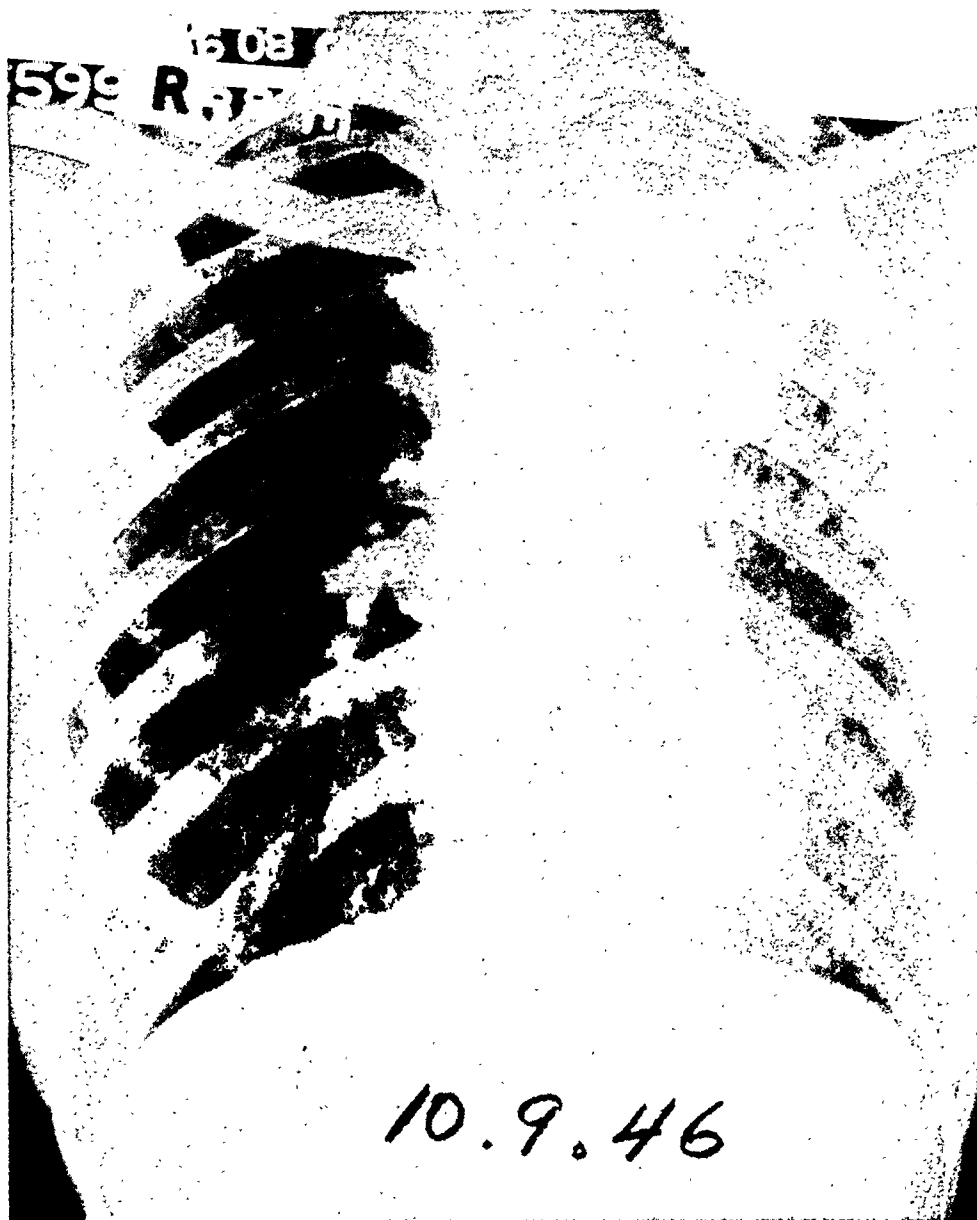


FIG. 8b. Patient C.St., chest roentgen-ray before treatment.

from a patient whose disease had regressed, or been converted by surgical collapse, to a state of non-infectiousness. In the remaining seven cases, however, the discharge of drug-resistant bacilli persisted throughout therapy and the post-treatment period of observation. During the first month of streptomycin therapy all of these seven patients had shown evidence of im-

provement although the change noted in one individual was not marked (figure 8). At a variable interval after the first appearance of drug-resistant bacilli, all seven cases resumed a progressive course. In four, the resumption of progression occurred during antimicrobial therapy and in the other three



FIG. 8c. Patient C.St., after three months of treatment showing progression which occurred after development of bacterial resistance.

shortly after the cessation of therapy. In all seven the re-institution or continuation of streptomycin (3.0 grams daily) had no discernible effect upon the course. The tuberculosis continued to progress and in four instances the disease terminated fatally.

*Histopathologic Observations.* Postmortem examinations were performed on only two patients, both of whom had been discharging strepto-

mycin-resistant tubercle bacilli for several months before death. Study of the tissues revealed the characteristic changes of pulmonary tuberculosis without any unusual features which could be attributed to the streptomycin therapy.

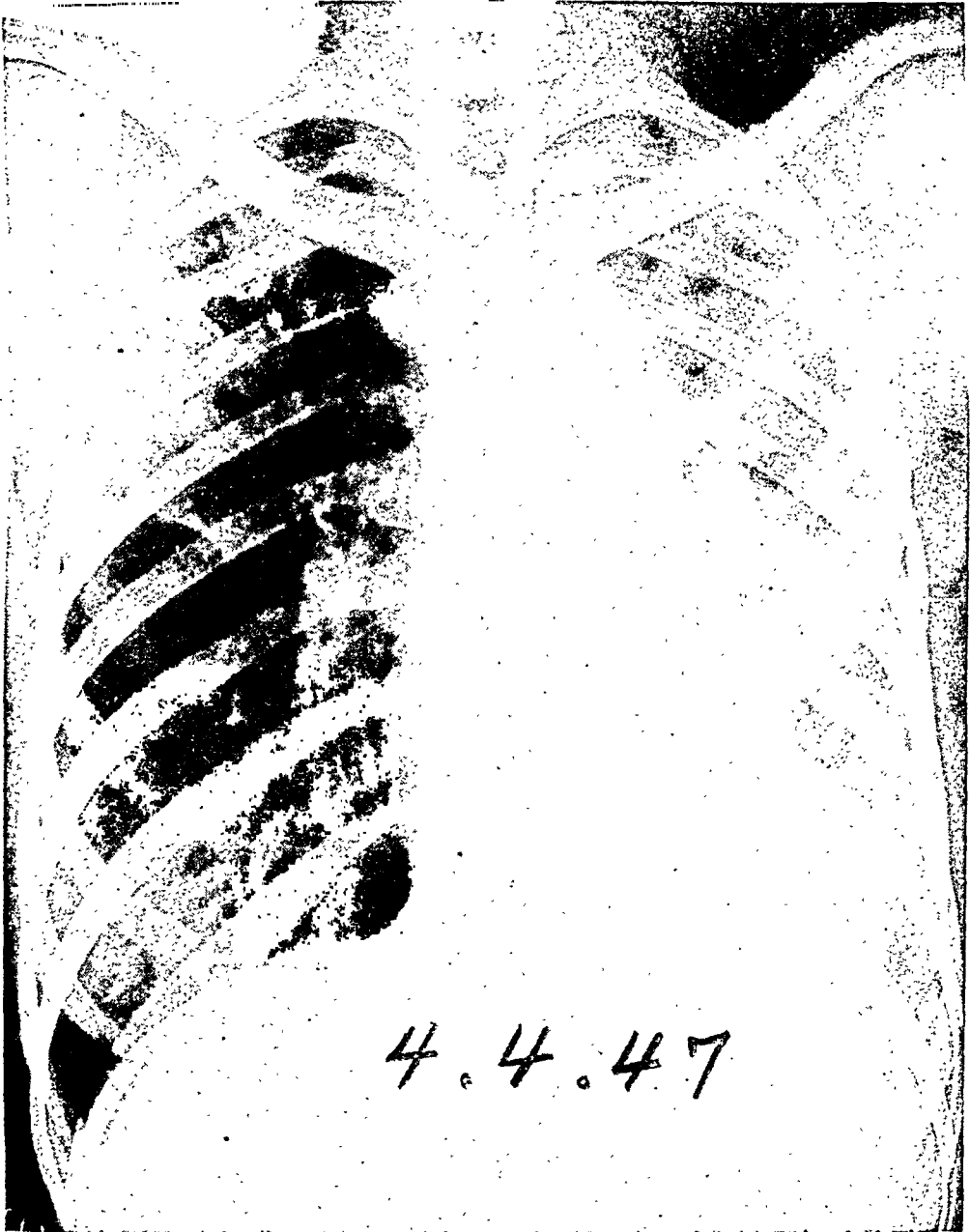


FIG. 8d. Patient C.St., further progression, uninfluenced by re-treating with streptomycin.

#### DISCUSSION

It has been established both in experimentally infected animals<sup>6</sup> and in patients with the generalized hematogenous or the meningeal forms of the



disease<sup>1, 3</sup> that streptomycin can exert an effect upon tuberculous infections *in vivo*. Moreover, in these investigations a definite effect upon disseminated tubercles in the lung was noted. Thus it can also be considered to be established that streptomycin is capable of exerting its antimicrobial action on at least one type of tuberculous lesion in the lung.

In contrast to the conditions which obtain for miliary tuberculosis, it is extremely difficult to evaluate the effect of an antimicrobial agent upon tuberculous processes which are chiefly limited to the lung. The course of pulmonary tuberculosis is variable, and there is no certain method by which to predict the degree of resistance which may be displayed by an individual patient.

Speedy and extensive resolution even of large and well-established exudative lesions occasionally occurs on a regimen of bed rest. Thus, in an individual patient, it is not possible to relate with certainty an unusually rapid resolution to the administration of an antimicrobial agent. More convincing evidence that there is a causal relationship between the drug and healing is the demonstration that regressive changes appear *with regularity* after it is administered. In the 43 patients with pulmonary tuberculosis in the present study, the institution of streptomycin therapy was followed in every instance by a measurable degree of clinical, roentgenologic or bacteriologic improvement in the status of the infection. The degree of improvement was only slight or temporary in some instances, whereas in others it was considerable and sustained. There were no cases treated, however, in which improvement of some degree failed to occur.

Extensive resolution and an appreciable reduction in cavity size during streptomycin therapy was observed in 15 of 18 patients with predominantly exudative pulmonary tuberculosis of moderately advanced or far advanced extent. In nine of the group, the improvement continued to the point of cavity closure and reversal of infectiousness during or shortly after the period of antimicrobial therapy. A similarly satisfactory status was attained by another five patients when the streptomycin treatment was followed by appropriate collapse therapy. All of the latter group had been considered unsuitable subjects for collapse therapy at the time antimicrobial therapy was started. Less striking changes were observed after streptomycin therapy in 18 patients with fibro-cavernous disease of long standing. Even among this group, however, cavity closure and sputum conversion occurred in four instances, retrogressive changes were observed in most of the others, and complete healing occurred in all of eight cases of laryngeal or tracheo-bronchial disease.

Thus on the basis of the regularity with which improvement occurred after the administration of streptomycin, it would seem that the beneficial results noted in this series of 43 patients with pulmonary tuberculosis were definitely attributable to the drug therapy.

In tuberculosis, as in other infections, healing presumably proceeds by essentially the same mechanisms whether the inhibition of the infection

results from antimicrobial therapy or is accomplished by the natural defenses of the host. Thus it would not be anticipated that the results attainable by the streptomycin therapy of pulmonary tuberculosis would be significantly superior to the most successful results ever observed previously in the natural healing of the disease. The principal effect of chemotherapy should be to produce a material increase in the number of such successful results and possibly to shorten the average time required for their accomplishment.

Recently developed tuberculous lesions may differ widely in character from a predominantly exudative to a predominantly proliferative process. In either type of lesion, the speed with which a significant degree of necrosis may occur, varies considerably. In general, however, the extent of tissue necrosis bears a relationship to the duration of the lesion. It would seem that the degree to which a particular lesion would be reversible by antimicrobial therapy (or by the natural forces of immunity) is largely determined by the amount of necrosis which had already occurred when the progress of the infection had been halted.

In extensive studies of the natural healing of exudative lesions, Amberson<sup>7</sup> has noted that a virtually complete resolution of the outer zone of the lesion may occur. Resolution does not occur, however, in the central and oldest portion of the lesion which is almost invariably necrotic by the time the total lesion is first detectable. The subsequent course of the infection thus depends to a large extent upon the size and the ultimate fate of the necrotic residue. It may be discharged through a bronchus, thus leaving a residual cavity which, if sufficiently small, may heal promptly. In other instances, the residual lesion may be encircled by fibrous tissue and eventually calcified in whole or in part. In either event, a focus of infection, which may even be undetectable roentgenologically, persists for a period measurable in years after the complete resolution of what was perhaps the major portion of the lesion.

In the present investigation, the course of the predominantly exudative lesions under streptomycin therapy has followed the exact sequence of events described by Amberson for the corresponding stages in the natural resolution of such lesions. In most instances, areas of pneumonia of variable size have contracted to a large degree leaving a residual core of consolidated lung or a constricted or apparently closed cavity. In other pneumonias in which the areas of caseation apparently represented a major portion of the total lesion, many large areas of excavation appeared during antimicrobial therapy. It is probable that the subsequent behavior of the residual lesions will be much the same as occurs under comparable conditions in the natural history of the disease.

It is not possible at this time to estimate the degree of reversibility of recently developed proliferative lesions because of the well recognized difficulty in distinguishing them from the exudative type of process during life. From the histopathologic observations in streptomycin-treated generalized hematogenous tuberculosis<sup>1</sup> and from experiments in guinea pigs,<sup>6</sup> it seems

likely that proliferative lesions are reversible to a considerable degree. Presumably in this type of lesion also, the extent of the necrosis present before antimicrobial therapy is the factor which determines the maximal attainable result.

It is not surprising that only a slight degree of improvement was observed in most of the streptomycin-treated patients who had chronic disease with established secondary fibrotic changes. In this stage of tuberculosis, the anatomic changes resulting from the reparative process itself constitute a barrier to the further healing of the lesions. Cavities are lined by walls of fibro-caseous tissue, often of considerable thickness. The lower ramifications of the bronchial tree may be so distorted or destroyed that proper drainage of areas of indolent caseating disease is not possible. Areas of recently developed disease may also be present as extensions of the chronic process. From the observations in the present study, it would seem that such areas of new involvement usually recede under antimicrobial therapy, but the underlying disease remains essentially unaffected.

In addition to the factors of tissue destruction and consequent anatomic distortions, there are other properties of tuberculous lesions which might condition the effectiveness of streptomycin. A most important question in this connection is whether the bacilli have unimpeded access to the drug in all types of pulmonary lesions.

It is probable that the actual physical penetration of the lesion by the drug is accomplished in virtually all instances. It has been demonstrated<sup>8</sup> that proliferative and fibro-caseous tubercles are readily penetrated by a variety of colloidal dyes and sulfones. As streptomycin, in the dosages in general use, is apparently freely distributed throughout the extracellular fluid of the body (central nervous system excepted),<sup>9</sup> it is reasonable to assume that it penetrates all viable inflammatory tissue in the lung including the walls of tubercles. Moreover, the high incidence of the appearance of streptomycin-resistant strains of tubercle bacilli in patients with chronic cavities suggests that the organisms within the lumen of the cavity have been in contact with the drug.

Even though physical penetration of all lesions presumably occurs, however, the particular type of lesions present might exert a considerable influence on the activity of the drug. It is known that the antimicrobial activity of streptomycin may be appreciably reduced by reduction in the pH of the environment to below 6.0.<sup>10</sup> If the pH of the exudative tuberculous lesion is essentially the same as in other pneumonic exudates (pH 6.7 to 7.1),<sup>11</sup> it would be in a range of high streptomycin activity. In contrast, a large area of tuberculous caseation would be considerably more acid. Moreover, such a large area of caseation might conceivably hinder diffusion and otherwise interfere with the activity of the drug. It should be noted that these possible effects of a large area of caseation on drug activity should also operate to interfere with the natural defenses of the host.

The relative importance of intracellular and extracellular bacilli in the

intensity of the infection and their respective vulnerability to the drug are fundamental questions in consideration of streptomycin activity at the site of the lesion. It is well recognized that many of the bacilli in a tuberculous lesion are situated within the monocytes. Information is limited concerning the relative proportions of intracellular and extracellular organisms in the various types of lesions. It is probable, however, that extracellular proliferation of bacilli is most prominent in the rapidly progressing lesions. These extracellular organisms should have easy access to streptomycin. In contrast, it is not known whether the bacilli within the monocytes can be reached by the drug. If the drug does not have access to the organisms its field of action would be limited to the bacilli multiplying extracellularly and such organisms as are freed from disrupted monocytes. It is conceivable, therefore, that the principal action of streptomycin consists of an interference with the proliferation of the extracellular component of the infecting population and that the phenomena of "crisis" and rapid resolution are direct consequences of such an action. A change in the host-parasite relationship of this general type may represent the maximal effect attainable from the use of this antimicrobial agent.

The possible relationship between a sudden inhibition of bacterial multiplication and the appearance of abrupt defervescence was discussed in a previous communication.<sup>1</sup> The same phenomenon of "crisis" which was observed in generalized hematogenous infections, also occurred in certain of the patients with acutely progressive exudative lesions in the lung (figure 5a).

The important influence of the nature of the lesion on the results attainable from the use of streptomycin is by no means unique to the antimicrobial therapy of tuberculosis. For example, the nature of the lesion plays an important rôle in determining the different end results usually observed after the antimicrobial therapy of the pulmonary infection caused by *Pneumococcus* and that produced by *Klebsiella*. Agents are available (sulfadiazine, penicillin, streptomycin) which are highly active on one or both of these two bacterial species both in vitro and in vivo. In pneumococcus pneumonia, the destruction of lung tissue is negligible, and powerful defenses are available or can be readily mobilized for the maintenance of a drug-induced remission. As a consequence, the administration of antimicrobial therapy at any stage of the disease short of terminal respiratory or vascular failure is usually followed by prompt recovery with restitution of the pulmonary tissues to their pre-disease state. In contrast, in *Klebsiella* pneumonia it is not usually possible to attain such a satisfactory result when antimicrobial therapy is started subsequent to the first few days of the acute infection. In this infection, a considerable destruction of lung tissue may occur rapidly, sometimes within 24 or 48 hours of onset. Once a significant degree of destruction has occurred, the subsequent control of the infection either by the defenses of the host or by antimicrobial therapy usually results in a chronic disease with a variable degree of pulmonary damage.

The relative importance of a drug which is antimicrobial in vivo, in the treatment of a particular infectious disease, is conditioned not only by the nature of the lesions but also by the speed with which a significant degree of resistance can be mobilized by the host. Obviously, it is this latter factor which determines the ideal length of the period during which chemotherapy should be administered. Thus far, even in the most successful of the streptomycin-treated cases of pulmonary tuberculosis, the arrest of the infection presumably was not accompanied by an eradication of tubercle bacilli from the lungs. Moreover, it is not to be anticipated, except under the most unusual circumstances, that such a total eradication of bacilli would occur during or immediately after streptomycin therapy. Aside from the questions of resistant strains of bacilli or the toxicity of the drug, it would obviously not be practicable to administer streptomycin for the period of years during which tubercle bacilli may persist in arrested lesions. Thus the success of streptomycin therapy rests on the ability of the patient to control the infection after the administration of the drug has been discontinued.

At present, there is no way in which the status of host resistance, or more precisely, the host-parasite relationship, can be accurately evaluated other than by observation of the outcome of the infection. It is known that certain individuals have shown evidence of the operation of impressive forces of resistance during the several months after the appearance of relatively extensive exudative-type lesions. There is no information, however, as to whether such rapidly operative resistance is an exceptionally rare phenomenon or whether it would be as quickly evident in most patients if the progress of the infection were reversed by antimicrobial therapy. In the present small series, the appearance of relapse while still on bed rest in two patients who had attained remissions during streptomycin therapy, is evidence that in some instances several months of streptomycin therapy are insufficient to ensure sustained control of the infection. Conversely, considerable hope is afforded by the fact that relapse has not occurred during the period of observation in the majority of streptomycin-treated pulmonary infections which have attained remission, both in the present study and in that of Hinshaw and Feldman. Moreover, in several of our patients extensive roentgenologic clearing with reversal of infectiousness occurred during the four to eight weeks after the cessation of streptomycin therapy. As most of these infections were actively progressing at the time antimicrobial therapy was started, it would seem that they represent examples of the ready operation of host resistance once the progression of the infection has been artificially checked.

It should be noted that, with the exception of an initial infection with *M. tuberculosis*, it is not definitely established that an important degree of host resistance actually *develops* during the months or years after the appearance of a progressive pulmonary lesion. The possibility exists that the observed phenomena of host resistance (or change in the balance of host-parasite relationship) do not develop, but are merely revealed, when

the onward progress of the infection has been suddenly checked by chemotherapy. In either event, however, it is likely that the chance for the maximum effectiveness of the host-defenses would be considerably enhanced the longer they were free to operate against an artificially inhibited infection.

Thus, from a consideration of both the nature of tuberculous lesions and the poorly understood variables of the host-parasite relationship, it is apparent that the ideal procedure in the chemotherapy of tuberculosis would be to administer the drug for many months.

In the present study, the administration of streptomycin for periods of three to four months to patients who continued to discharge *M. tuberculosis* was accompanied in all but one instance by the appearance of organisms which were highly resistant to streptomycin in vitro. In a previously reported study<sup>1</sup> of the streptomycin treatment of generalized hematogenous tuberculosis, it was observed that, under the conditions of the test as employed in this laboratory, the appearance of bacilli which were drug-resistant in vitro indicated the presence of streptomycin-resistant infections in vivo.

Unlike generalized hematogenous tuberculosis, it would not be anticipated that relapse would inevitably occur in pulmonary tuberculosis merely because of the appearance of drug-resistant bacilli. Improvement continued in four patients of the present study after drug-resistant organisms were isolated, and sputum conversion occurred despite the development of resistance. In those instances, however, the extent and rapidity of the initial improvement had been most noteworthy or the cavitary source of possible new bronchiogenic disseminations had been obliterated by collapse therapy.

Another factor which makes correlation of in vitro and in vivo bacterial sensitivity difficult in pulmonary tuberculosis is the phenomenon of delayed roentgenologic clearing mentioned previously. During the third and fourth months after the start of streptomycin therapy, extensive roentgenologic clearing may occur even though the administration of the drug is discontinued on the forty-second day of treatment. If such delayed roentgenologic clearing appeared in a patient in whom chemotherapy had been continued, it might easily be assumed that the improvement was related to the continued administration of the drug. Moreover, if such a patient were discharging streptomycin-resistant bacilli during the last one or two months of therapy, it would be easy to arrive at the false conclusion that the infection was still streptomycin-sensitive in vivo.

In the present study there were only seven patients who continued to discharge bacilli throughout and subsequent to the streptomycin treatment. All of them had shown definite evidence of some regression of the infection during the first weeks of streptomycin therapy at a time when their organisms were highly sensitive to the drug in vitro. At a variable interval after the first detection of drug-resistant bacilli, the tuberculous infections again became actively progressive. In every instance, the newly progressive infections were completely uninfluenced by the further administration of streptomycin and four of these patients have died.

It would seem, therefore, in pulmonary tuberculosis, as in generalized hematogenous tuberculosis, that the discharge of bacilli which are streptomycin-resistant in vitro, indicates the presence of a drug-resistant infection in vivo. The only difference in the significance of the phenomenon in the two types of infection is that relapse does not necessarily follow its appearance in pulmonary tuberculosis. It also appears that the incidence of bacterial resistance is directly related to the duration of therapy. In both types of tuberculosis streptomycin-resistant tubercle bacilli appeared in the great majority of patients from whom organisms could be obtained after three months of streptomycin therapy. Moreover, in some individuals the appearance of drug-resistant organisms was detected as early as the second month of chemotherapy. On the basis of these observations, it appears that the period during which streptomycin exerts antimicrobial activity in tuberculosis terminates in most infections some time between the sixtieth and the ninetieth days of therapy. Thus the range of the period during which the administration of streptomycin serves a useful purpose is sharply limited.

As pulmonary tuberculosis treated by any method has a pronounced tendency toward relapse, it is advisable to attempt to avoid the emergence of strains of tubercle bacilli which are predominantly streptomycin resistant. One method by which this might be accomplished would be to administer the drug for a total period of two months or less. On the basis of preliminary experience, it would seem that with the 42 day regimen in use in this study, the incidence of streptomycin-resistance is drastically lowered but that its development is by no means completely eliminated. There has not been sufficient experience as yet with the one gram daily dose of streptomycin to determine whether the incidence of bacterial resistance is related to the size of the daily dose as well as to the duration of treatment. Moreover, there has been no opportunity to observe the incidence of bacterial resistance in patients who have received two 42 days' courses of streptomycin separated by an interval of several months.

*Value of Streptomycin in Pulmonary Tuberculosis.* Although the greatest value of streptomycin is clearly in relatively acute processes which can be materially influenced by a relatively short period of antimicrobial therapy, the drug is of important though limited value in certain cases of chronic tuberculosis. In a few instances, notably in slowly progressive chronic lesions which are presumed to be chiefly proliferative, marked regression may take place during or shortly after the completion of streptomycin therapy. The principal value of the drug in chronic tuberculosis, however, will probably be in the treatment of laryngeal and tracheo-bronchial complications and as an adjunct to surgical therapy.

Tuberculous involvement of the larynx or bronchi usually represents a potentially serious complication of pulmonary tuberculosis. Without antimicrobial therapy, the ulcerative lesions of these structures have a tendency toward slow progression. Although natural healing occurs, it is slow and uncertain. Moreover, because the spontaneous healing of tracheo-bronchial

lesions is always protracted, the resulting distortion of the airway may considerably complicate the underlying pulmonary infection. Thus the rapid healing of laryngeal and tracheobronchial tuberculosis which has been observed almost uniformly after the administration of streptomycin, represents a notable advance in tuberculosis therapy. It must be appreciated, however, that, unless the underlying pulmonary tuberculosis is also controlled, the laryngeal or tracheobronchial disease is likely to recur with drug-resistant organisms.

The introduction of an antimicrobial agent effective against *M. tuberculosis* inevitably enlarges the number of cases in which surgical therapy is feasible. It is probable that the principal use of streptomycin in the treatment of chronic fibrocavernous tuberculosis will be as an adjuvant to surgery. In any form of tuberculosis, however, the frequency with which drug-resistant strains of tubercle bacilli appear is such that the administration of streptomycin will evidently have to be properly timed in relation to the planned operative procedures. Retrospectively it is apparent that in some of the cases in the present study opportunities were missed for surgical treatment. This was true particularly among those treated early in the study before the correlation between the appearance of drug resistance and loss of therapeutic effectiveness was evident. Later, in several cases whose initial improvement was considerable, yet apparently had not sufficient momentum to attain a satisfactory remission without mechanical measures, thoracoplasties were performed within 12 to 16 weeks after the start of antimicrobial therapy. The results were encouraging in these few instances, considering especially the character of the original disease. It is possible that in some situations, in which the necessity for surgical collapse is clearly apparent from the start, the best results will be obtained by operating early in the course of streptomycin. On the other hand, there are no certain criteria for predicting, at any time prior to a reversal of the favorable trend, the ultimate improvement which may follow streptomycin. Reference has already been made to a few cases in which with only slight early improvement the total regression after several months was unexpectedly satisfactory. The time at which the patient's condition is optimal for necessary surgery can, therefore, not always be easily determined.

Another field in which streptomycin may be useful in conjunction with surgery is as a prophylactic agent against the extensions of the disease which occasionally occur as a complication of thoracoplasty. A large scale investigation of this type of regimen is in progress in the Veterans' Administration.<sup>12</sup>

At the present time it would seem proper to administer streptomycin to cases of progressing moderately advanced or far advanced pulmonary tuberculosis of recent origin and in which the disease is of predominantly exudative character. In chronic cases, in which extensive fibrotic changes have already occurred, streptomycin should not be used until the timing of its administration has been carefully considered in relation to possible sur-



gical therapy. Otherwise, the usual result will be merely the emergence of a drug-resistant strain of organisms in a patient who has attained only a short-lived period of improvement. It also seems proper to administer streptomycin to patients with ulcerating laryngeal or tracheo-bronchial tuberculosis. Occasionally with such involvement the underlying pulmonary process is so extensive that arrest by any combination of therapeutic measures seems highly unlikely. In this situation, it may be advisable to administer the streptomycin in short (two week) courses in an attempt to obtain symptomatic relief while avoiding the appearance of bacterial resistance.

Because of neurotoxicity, streptomycin should not be used in the treatment of patients with pulmonary tuberculosis of minimal extent, or in patients with more advanced disease in which the outlook is favorable with conventional methods alone. Even if it should be established that satisfactory therapeutic efficiency and a low incidence of neurotoxicity occur when the total daily dose of streptomycin is limited to only one gram, the problem of drug-resistance remains a deterrent to the unrestricted use of this antimicrobial agent. There is no indication that arrest of tuberculosis accomplished with the aid of streptomycin is free of liability of relapse, any more than arrest resulting from spontaneous healing. To use the drug unnecessarily, even though the immediate result be good, may amount to wasting a therapeutic resource for which there is possibility of later need.

### SUMMARY

The administration of streptomycin for periods of 42 to 120 days to 43 patients with pulmonary tuberculosis was followed, in every instance, by some degree of measurable improvement in the status of the disease. Of 18 patients, followed six weeks or longer after treatment, whose pulmonary lesions were predominantly exudative in nature, nine attained satisfactory early remissions during or shortly after the cessation of the antimicrobial therapy. Of these, two relapsed within six months, requiring collapse therapy, and a third relapsed within 12 months. Another six patients showed considerable improvement under streptomycin therapy, but fell short of attaining full remission. The suitability of these cases for collapse therapy, however, was appreciably enhanced and this was subsequently undertaken in five with apparent success. In three patients there was no significant benefit and a short period of symptomatic improvement was followed by early resumption of the progressive course of the infection.

Less striking changes were observed in another 18 patients, also followed six weeks or longer, with chronic fibrocavernous disease. Four had fully satisfactory early responses and four more attained favorable results when the antimicrobial therapy was followed by thoracoplasty. In 10 of the 18 cases there was a short period of temporary improvement but no lasting benefit. Strains of tubercle bacilli which were highly resistant to the action of streptomycin in vitro were obtained from 10 of 11 patients who continued

to discharge bacilli during 75 to 120 days of chemotherapy. The incidence of drug-resistant strains of bacilli was much lower when streptomycin therapy was continued for only 42 days. In every instance in which relapse occurred after the appearance of streptomycin-resistant organisms, the course of the infection was completely uninfluenced by the further administration of streptomycin.

### CONCLUSIONS

1. The administration of streptomycin to patients with pulmonary tuberculosis is followed by a definite effect upon the course of the infection. The magnitude and the durability of the effect depend upon the nature of the lesion, the status of the host-parasite relationship, and the length of time the infecting organisms remain streptomycin-sensitive.

2. In pulmonary tuberculosis, as in generalized hematogenous tuberculosis, the appearance of streptomycin-resistant organisms (under the conditions of the test employed) indicates the presence of an infection which is drug-resistant *in vivo*.

### BIBLIOGRAPHY

1. McDERMOTT, W., MUSCHENHEIM, C., HADLEY, S. J., BUNN, P. A., and GORMAN, R. V.: Streptomycin in the treatment of tuberculosis in humans. I. Meningitis and generalized hematogenous tuberculosis, *Ann. Int. Med.*, 1947, xxvii, 769-822.
2. HINSHAW, H. C., and FELDMAN, W. H.: Streptomycin in treatment of clinical tuberculosis: A preliminary report, *Proc. Staff Meet., Mayo Clinic*, 1945, xx, 313-318.
3. HINSHAW, H. C., FELDMAN, W. H., and PFUETZE, K. H.: Treatment of tuberculosis with streptomycin, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 778-782.
4. PFUETZE, K. H.: Personal communication.
5. HINSHAW, H. C.: Personal communication.
6. FELDMAN, W. H., and HINSHAW, H. C.: Effects of streptomycin on experimental tuberculosis in guinea pigs: A preliminary report, *Proc. Staff Meet., Mayo Clinic*, 1944, xix, 593-599.
7. AMBERSON, J. B., JR.: The process of resolution in pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1936, xxxiii, 269-301.
8. RICH, A. R.: The pathogenesis of tuberculosis, 1944, Charles C. Thomas, Springfield, Illinois, 726.
9. BOXER, G. E., JELINEK, J. C., DuBOIS, R., TOMPSETT, R., and EDISON, A. D.: Chemical determination of streptomycin in the blood following intramuscular injection, *Jr. Pharm. and Exper. Therap.*, in press.
10. WAKSMAN, S., and SCHATZ, A.: Streptomycin: origin, nature and properties, *Jr. Am. Pharm. Assoc. (Sci. ed.)*, 1945, xxxiv, 273.
11. KELLEY, W. H., SCADRON, E. N., and SHINNERS, B. M.: Hydrogen ion concentration in exudates of pneumococcus infection, *Jr. Exper. Med.*, 1938, lxxvii, 659-665.
12. A preliminary statement concerning the effects of streptomycin upon tuberculosis in man: Office of Chief Medical Director, Veterans' Administration, the Surgeon General of the Army and the Surgeon General of the Navy, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 634.

# CASE REPORTS

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## CHRONIC PORPHYRIA \*

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THE clinical picture and criteria for the diagnosis of porphyria, congenital or acute, have been adequately discussed in the recent literature. The rarity of the disease and the failure of many physicians to be acquainted with it are factors undoubtedly causing many cases to be overlooked at the present time. We are reporting this case because of its chronicity, a point which is not emphasized in most discussions, and because of the presence of extreme pigmentation and definite neurological involvement.

### CASE REPORT

Mrs. D. B., a 44 year old white housewife, was first admitted to the Albany Hospital on February 4, 1945 with the complaints of vaginal bleeding; frequent, painful urination; and occasional inability to void, of several months' duration. Previous to the onset of the present illness she had always enjoyed good health with the exception of three miscarriages prior to the birth of her son, now 14 years old. Following this delivery, she and her family noted that her skin was turning dark, but not being otherwise inconvenienced, she did not seek medical advice. She stated that for the last few years she had had spells of crying and nervous tension.

Physical examination on this admission revealed a woman who looked older than the stated age and whose skin was heavily pigmented, especially the nose and cheeks. Pelvic examination showed an irregularly enlarged uterus but the remainder of the physical examination was not remarkable. Routine urine and blood studies were normal. On the second hospital day, a pan-hysterectomy, right salpingo-oophorectomy and appendectomy were performed with removal of a fibroid uterus. Post-operatively, her course was marked by almost daily attacks of nausea and vomiting for 15 days. A urine examination during this time was noted to be mahogany-colored and the nurses' notes report the urine to be very dark reddish-brown on another occasion. She was discharged on the nineteenth hospital day to the care of her family physician.

At home, she was confined to bed, being extremely weak, scarcely able to lift her arms or legs. Her appetite was very poor and she vomited frequently but had no abdominal pain, constipation, diarrhea or urinary difficulties. She was treated by her doctor with parenteral liver extract and adrenal cortical extract but failed to show any improvement. Because of lack of response to the adrenal cortical extract, a blood pressure of 140 to 160 mm. Hg systolic and 100 to 120 mm. diastolic, and persistence of dark-colored urine, the tentative diagnosis of Addison's disease was doubted and the patient returned to the hospital for further study.

*Second Hospital Admission* (March 25, 1945). The chief complaints on admission were extreme weakness of arms, legs and neck; recurrent nausea and vomiting; weight loss of 30 pounds since the previous hospitalization.

*Family History.* The family history was non-contributory. There were eight siblings living and well.

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From the Department of Medicine, Albany Hospital, Albany, N. Y.

*Past History.* Previous to the present illness there was no history of abdominal pain, nausea, vomiting, weakness or dark-colored urine. The patient had not been taking drugs of any kind and there had been no known exposure to lead or to arsenic.

*Physical Examination.* Temperature 99.0°; pulse 128; respirations 32. As on the previous admission, the patient appeared much older than the stated age. Her skin was deeply pigmented over the whole body but especially over the face where the nose and malar eminences were actually black (figure 1). There was moderate hypertrichosis over the lateral frontal areas. The pupils were round, regular and equal; they reacted to light and accommodation. There was no nystagmus. The upper incisor teeth were brownish in color and protuberant. There was no abnormal pigmentation of the mucous membrane of the mouth except for a single, small, dark brown spot 4 mm. in diameter on the lower lip. The neck muscles were weak. The



FIG. 1. Appearance of patient contrasted with that of a normal young adult. Note generalized pigmentation of skin with concentration over nose and cheeks; the prominent brownish-colored incisor teeth. The hypertrichosis over the lateral frontal areas is not clearly shown.

thyroid was not palpable. The lungs were normal to percussion and auscultation. The heart was not enlarged to percussion; the rate was rapid with normal rhythm; there were no thrills or murmurs. The blood pressure was 160 mm. Hg systolic and 100 mm. diastolic. The abdomen presented a well-healed midline, operative scar; no organs or masses were palpable.

The tissues of the abdomen showed considerable weight loss and there was marked wasting of the extremities and atrophy of all muscles but especially of the interossei and of the thenar eminence of the right hand and of the left gastrocnemius. There was generalized weakness of all extremities with a foot drop on the left. The reflexes were as follows: the triceps and biceps were weak but obtainable; the radial, abdominal, knee and ankle reflexes were absent. No pathological reflexes were present. There was no astereognosis and the proprioceptive reflexes were intact. Perception to pinprick was diminished over the distribution of the right ulnar nerve and increased over the course of the left peroneal nerve.

*Laboratory Data.* The urine was reddish-brown in color; sugar 1+. The total coproporphyrin in a 24-hour urine specimen of 565 c.c. was 407 gamma (normal

values are under 100 gamma). Nearly all of this excess of porphyrin was the type III isomer so that the findings are qualitatively and quantitatively abnormal. There was no uroporphyrin and the porphobilinogen test was likewise negative.\* Hemoglobin 12.0 gm.; red blood cells 4,000,000 per cu. mm.; white blood cells 8,000 per cu. mm. The differential count was essentially normal. Blood Wassermann negative. Non-protein nitrogen 53 mg. per cent; uric acid 7.0 mg. per cent; icteric index 13; serum bilirubin 1.3 mg. per cent; serum proteins 6.2 gm. per cent with albumin 2.8 gm. per cent and globulin 3.4 gm. per cent. Glucose tolerance test showed fasting blood sugar of 101 mg. per cent;  $\frac{1}{2}$  hour: 209 mg. per cent; 1 hour: 229 mg. per cent; 2 hours: 197 mg. per cent. Serum sodium 429.3 mg. per cent; serum potassium 30.6 mg. per cent and serum chlorides 420 mg. per cent.

A chest roentgen-ray showed a small, discrete nodular area at the right lung base with some fibrosis just above the diaphragm, interpreted as some former inflammatory change, or a possible metastatic nodule. The cardiac shadow was normal in size. A flat plate of the abdomen revealed a ring-like shadow in the region of the gall-bladder, but no visible calcification in either adrenal gland. An electrocardiogram showed a normal sinus rhythm with a rate of 118. AV, QRS and ST times were normal. ST<sub>1</sub> and 2 were slightly depressed; T<sub>1</sub> low; T<sub>2</sub> diphasic; R<sub>3</sub> low and slurred; T<sub>3</sub> inverted. The changes in the ST lines and T-waves were believed possibly due to fatigue from the rapid rate. Biopsy of the skin from the abdomen showed an iron-free pigment disposed in normal fashion in the lowest layer of the epidermis.

*Course.* While in the hospital, the patient showed very little change in the neurological findings. Emotional instability was not noted, and symptoms of bulbar involvement did not appear. Nausea and vomiting occurred on two or three occasions during the first few hospital days, clearing spontaneously thereafter. Parenteral vitamins were administered daily. She was discharged on the twelfth hospital day to be followed by her local physician.

### DISCUSSION

It has been customary to classify porphyria as either congenital, acute or chronic.<sup>1</sup> In congenital porphyria, the onset is usually in males in infancy or early childhood; there is great sensitivity to light and uroporphyrin type I is usually excreted in large amounts in the urine. In the acute form, the onset is usually in females in the third to fifth decades, there is little or no light sensitivity and uroporphyrin type III is found in the urine in excessive amounts. Intermediate is a group which has been called "chronic porphyria" where either a type I or III uroporphyrin or coproporphyrin is excreted. The skin is somewhat sensitive to light and symptoms referable to the gastrointestinal tract are present.

The problem of porphyria may be regarded as an "inborn error of metabolism" and probably not limited only to the stage of acute symptoms.<sup>2</sup> There are two porphyrins that are important in cases of porphyria, uroporphyrin which is found in small amounts in normal urine, and coproporphyrin which is found in small amounts in normal feces. Only two isomer types, namely I and III, of these porphyrins occur in nature. One of the most reasonable theories as to the pathogenesis of the disease is that during the formation of hemoglobin, the metabolism of porphyrin remains at an embryonic level.<sup>3</sup> Although the disease is a chronic metabolic disorder and it has been shown that uroporphyrin may be excreted by patients between attacks,<sup>4, 5, 3</sup> the cause of the acute attacks is not definitely known.

\* We are greatly indebted to Dr. C. J. Watson of the Medical School of the University of Minnesota who was kind enough to make the analysis for porphyrin in the urine.

Since the opportunity to observe a patient with porphyria is not often presented, we would like to point out briefly the important features in the clinical types.

Congenital porphyria is frequently familial.<sup>3, 6</sup> Only one case of apparent hereditary transmission (father to son) has been observed (Radaeli, cited by Mason et al.<sup>3</sup>). Turner and Obermayer<sup>7</sup> reviewed the literature up to January 1939 and found 86 cases of congenital porphyria with nine possible exceptions recorded. There were 56 males and 26 females in the series. The onset occurred in the first 10 years of life in 36 cases and in the majority of the remainder before 40 years of age. One case occurred in the sixth decade and another in the seventh decade. A familial incidence was recorded in 30 instances.

With rare exceptions, the earliest and most important sign is red urine.<sup>3</sup> This may precede the skin changes by weeks or years.<sup>6</sup> The excretion of colored urine may be intermittent or continuous. Attention may be called to the disease by the development of skin lesions on exposure to sunlight. Although this sensitivity to light is usually apparent in the early years of life, it may not appear until late. One of Gunther's patients showed no signs of photosensitivity until the fiftieth year.<sup>3</sup> The skin lesions have been described under the names "hydroa vacciniforme" or "hydroa aestivale" but not all of the reported cases of hydroa aestivale have exhibited porphyria. After exposure to sunlight, the skin eruption usually begins with a diffuse erythema followed by edema. A vesicular or bullous eruption may follow and if secondary infection occurs, pustules develop. Healing is accompanied by scarring and deformity. The scars usually become pigmented. When exposures are frequent, the finger tips, nose and ears may become deformed. Contracture of scar tissue may bring the upper teeth into view (figure 1). Generalized pigmentation of the skin is common and is frequently accompanied by hypertrichosis.<sup>6, 7</sup> The pigment is probably porphyrin. It has been found in the bones and teeth of patients who died from chronic porphyria.<sup>3</sup> The pigmentation differs from that seen in Addison's disease in that the mucous membranes are not involved.<sup>5</sup>

Up to 1939, over 250 cases of acute porphyria had been reported.<sup>1</sup> About 100 cases were classified as acute, toxic and 153 as acute, idiopathic porphyria.<sup>7</sup> These types are not distinguishable by clinical or laboratory methods and are classified as toxic if a noxious agent can be identified. Mason and his associates<sup>3</sup> found a barbiturate was the usual toxic agent since they showed that out of 100 cases, sulfonal was used in 68 and trional in 11. Veronal, lead, acetanilid and nitrobenzol are also stated to be associated with acute porphyria. However, they may be only precipitating factors. Acute porphyria may also be a congenital disorder for instances have been described where one member of a family had acute porphyria while another had the congenital type. It has been observed in three generations and is inherited as a Mendelian dominant.<sup>1</sup>

Turner<sup>4</sup> has shown that porphyria may be a persistence of a fetal pyrrol metabolism. He states that the metabolic fault is not limited to the period of acute symptoms and claims that acute idiopathic porphyria may be as much an inborn error of pyrrol metabolism as is congenital porphyria.

The idiopathic type has occurred as isolated instances although there is one exception, a family with three sisters, mother and grandmother.<sup>8</sup>

The acute attack is often preceded by an interval of general malaise with vague intestinal complaints, insomnia, nervousness and weakness as the chief symptoms.

The acute attack begins with abdominal pain which is colicky and severe. Nausea and vomiting are usually present. Of importance in differentiating these findings from an acute surgical abdomen is the lack of muscle spasm. Constipation is common. Roentgen-rays of the intestinal tract may show marked spasm of the ileum, while the stomach and colon may be dilated,<sup>6</sup> though there are exceptions to this. Chandler and his associates<sup>9</sup> report a patient with acute, idiopathic porphyria who had severe, cramp-like abdominal pain. Vomiting was frequent. A hard mass was palpable in the epigastrium. The clinical picture was one of a malignant growth but at operation the stomach was found to be in a state of extreme contraction producing the apparent tumor. There may be a fever of 100° to 102° and a leukocytosis of 15,000 to 20,000. The urine at this time is dark brown or reddish and porphyrin, or rarely the colorless porphyrinogen, is present.<sup>3</sup>

About one-half of the patients with acute toxic or idiopathic porphyria die of involvement of the central nervous system in an ascending or Landry type of paralysis.<sup>6</sup> Sensory disturbances, as hypesthesia and paresthesia, may be present. Hallucinations and delirium as well as apathy is seen.

Usually patients with acute porphyria excrete large amounts of uroporphyrin III and I in the urine with a great preponderance of the type III isomer. Usually only a small amount of coproporphyrin III is present in the urine.<sup>10</sup> There are, however, clear cut exceptions to this.<sup>2</sup> Fischer and Libowitzky<sup>11</sup> reported the first case of acute toxic porphyria with the excretion of uroporphyrin I, and Turner<sup>4</sup> reported the first case of the idiopathic type where this porphyrin was found.

Our patient is somewhat difficult to classify. This case is unusual in that deep pigmentation is present in conjunction with neurological involvement and coproporphyrin III was isolated from the urine. Sensitivity to light has not been observed in acute porphyria<sup>3</sup> but is found in the congenital type. On the other hand, symptoms referable to the central nervous system occur in many patients with acute porphyria.<sup>6</sup> Uroporphyrin, type I or III, is found in excessive amounts in congenital and acute porphyria, respectively. Coproporphyrin is found in large quantities in the urine of patients with many forms of hepatic disease,<sup>12</sup> including atrophic cirrhosis, infectious jaundice, obstructive jaundice and hemochromatosis. Our patient did not have any clinically demonstrable liver disease.

Dobriner and Rhoads<sup>1</sup> discuss a group of cases of porphyria which are classified as chronic. According to them, this term was first applied by Günther to cases with increased excretion of porphyrin, which could not be called either congenital or acute. The skin is somewhat sensitive to light and symptoms arising from the intestinal tract are present. Coproporphyrin III has been found in the urine, alone<sup>13</sup> and in combination with uroporphyrin I and III.<sup>1</sup>

Taylor and his associates<sup>14</sup> recently observed a woman with chronic porphyria exhibiting photosensitivity with abdominal pain, nausea and vomiting. Large amounts of coproporphyrin I and III were excreted in the urine for a period of over one year.

Our patient seems to fit in this classification. The late onset at age 34 and the duration over a period of 14 years are significant. The isolation of such large amounts of coproporphyrin III from the urine is uncommon in the absence of liver disease and excludes the diagnosis of acute or congenital porphyria.

One year after discharge from the hospital, a follow-up report was received from the patient's doctor who stated that she is gradually getting stronger. She can walk and feed herself and is able to work one-half a day at light housework. The pigmentation does not seem to be as dark. The reflexes are unchanged. There has been no abdominal pain, nausea or vomiting. Treatment has consisted of the administration of liver extract, vitamin B and iron.

### SUMMARY

An unusual case of chronic porphyria is presented, featuring striking, deep pigmentation of the skin, neurological changes and gastrointestinal symptoms. Coproporphyrin III was isolated from the urine. A brief review of the literature is included.

The authors are indebted to Dr. Thomas Ordway for permission to study this patient and for helpful criticism of the manuscript.

### BIBLIOGRAPHY

1. DOBRINER, K., and RHOADS, C. P.: The porphyrins in health and disease, *Physiol. Rev.*, 1940, xx, 416-468.
2. WATSON, C. J.: Porphyria, *South. Med. Jr.*, 1943, xxxvi, 359-363.
3. MASON, V. R., COURVILLE, C., and ZISKIND, E.: The porphyrins in human disease, *Medicine*, 1933, xii, 355-439.
4. TURNER, W. J.: Studies on porphyria. III. Acute, idiopathic porphyria, *Arch. Int. Med.*, 1938, lxi, 762.
5. NESBITT, S.: Acute porphyria, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 286-294.
6. WATSON, C. J.: The porphyrins and their relation to disease, *Oxford Med.*, 1938, Oxford Univ. Press, New York, iv, 1-34.
7. TURNER, W. J., and OBERMAYER, M. F.: Studies on porphyria. II. A case of porphyria with epidermolysis bullosa, hypertrichosis and melanosis, *Arch. Dermat. and Syph.*, 1938, xxxvii, 549-572.
8. BARKER, L. F., and ESTES, W. L., JR.: Family hematoporphyrinuria and its association with chronic fits and acute polyneuritis, *Jr. Am. Med. Assoc.*, 1912, lviv, 818.
9. CHANDLER, F. G., HARRISON, G. A., and RIMINGTON, C.: Clinical porphyrinuria with report of a case of the acute, idiopathic type, *Brit. Med. Jr.*, 1939, ii, 1173-1180.
10. NESBITT, S., and WATKINS, C. H.: Acute porphyria, *Am. Jr. Med. Sci.*, 1942, cciii, 74-83.
11. FISCHER, H., and LIBOWITZKY, H. L.: Auftreten von Uro-bzy. Koproporphyrin I bei akuter Porphyrie, *Ztschr. f. physiol. Chem.*, 1936, ccxli, 220-222.
12. NESBITT, S., and SNELL, A. M.: Excretion of coproporphyrin in hepatic disease. I. Correlation of urinary and fecal excretion with parenchymatous hepatic damage, *Arch. Int. Med.*, 1942, lxi, 573-581.
13. FISCHER, H., and DUESBERG, E.: Über Porphyrine bei klinischer und experimenteller Porphyrie, *Arch. f. exper. Path. u. Pharmacol.*, 1932, clxvi, 95-100.
14. TAYLOR, I. J., SOLOMON, M. L., WEILAND, G. S., and FIGGE, F. H. J.: Chronic porphyria, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 26-29.



## ACUTE HEMOLYTIC ANEMIA WITH AUTO-AGGLUTINATION FOLLOWING SULFONAMIDE THERAPY \*

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THE following case is reported because it represents a rare phenomenon previously described as a complication of sulfonamide therapy and as a potential source of error in blood typing.

A 23 year old soldier was admitted on January 7, 1945 with a gunshot wound through the left abdomen. Laparotomy revealed transection of the jejunum in two places and a perforation of the stomach. The exit wound was in the left lumbar region. The perforations of the stomach were sutured, the involved jejunum resected, and an end-to-end anastomosis done. Approximately 2,000 c.c. of blood were found in the peritoneal cavity. Four grams of sulfanilamide powder were placed into the peritoneal cavity, another four grams into the retroperitoneal space. Severe shock necessitated four transfusions, each of 500 c.c. of type "A" blood, and 750 c.c. of plasma on the day of admission. Cross matching with the donor's blood showed compatibility. There was no transfusion reaction.

On January 8 five grams of sodium sulfadiazine were given intravenously in conjunction with 3,000 c.c. of saline and one unit of plasma. Penicillin therapy was instituted, using 20,000 units every two hours. The patient's temperature ranged from 101 to 103° F. The blood count showed: Hemoglobin 85 per cent; erythrocytes 5,180,000. Leukocyte count was 6,000 with 65 per cent neutrophils and 35 per cent lymphocytes. The blood sulfanilamide level was 3.1 mg. per cent.

On January 9 the sulfonamide medication was discontinued because of a drop of the leukocyte count to 5,000. The sulfadiazine level was 9.2 mg. per cent. Penicillin, plasma and intravenous fluids were continued.

On January 10 a left pleural effusion developed, accompanied by a rise of temperature to 105°.

On January 13 the erythrocyte count had dropped to 2,750,000, the hemoglobin to 60 per cent. The leukocyte count was 7,200 with 67 per cent granulocytes and 33 per cent lymphocytes. Five hundred c.c. of type "A" blood were transfused without reaction.

A roentgenogram taken on January 15 showed decrease of the pleural effusion.

On January 18 an infected intraperitoneal hematoma was incised and drained. The erythrocyte count was 2,200,000, hemoglobin 50 per cent, the leukocyte count 7,000 with 68 per cent granulocytes. On this day jaundice was first noticed. The icteric index was 37.

Another transfusion was indicated. Cross-matching with type "A" blood from four different donors (slide technic at room temperature) showed agglutination only on the minor side (donor's serum with recipient's cells). Retyping the patient's cells with the standard rabbit antiserum now showed an apparent "AB" type. On cross matching, however, with several "AB" bloods there was incompatibility on the major and minor side. It was then found that the patient's serum agglutinated his *own* cells. This finding suggested the possibility of this being a case of hemolytic anemia with "cold" auto-agglutination as described by Antopol and his associates.<sup>1</sup> Retyping the blood at 37° showed type "A," no cross agglutination with other type "A" bloods, and no auto-agglutination.

Further relevant laboratory data obtained on January 19 were the following: Erythrocyte fragility: slightly decreased. Van den Bergh test: biphasic reaction.

\* Received for publication July 11, 1946.

Serum bilirubin: 7.5 mg. per cent. Blood culture: negative. The urine contained 3 plus albumin, increased urobilinogen (1:64), but no hemoglobin.

During the following 10 days the red blood count remained under 3,000,000 in spite of repeated blood transfusions which were given at body temperature with no untoward reactions. The icterus index reached its peak of 44 on January 22 and then decreased gradually.

On January 26 the leukocyte count had risen to 12,600 with 68 per cent granulocytes. Of these 15 per cent were band forms. Toxic granulation was present.

On January 29 the erythrocyte count was 3,060,000 and the icteric index 28. Auto-agglutination could no longer be demonstrated.

On February 6 a left subdiaphragmatic abscess was incised and drained. Subsequently the patient made a gradual recovery without any further incident. He received a total of 12 blood transfusions, 21 units of plasma, and 6,140,000 units of penicillin.

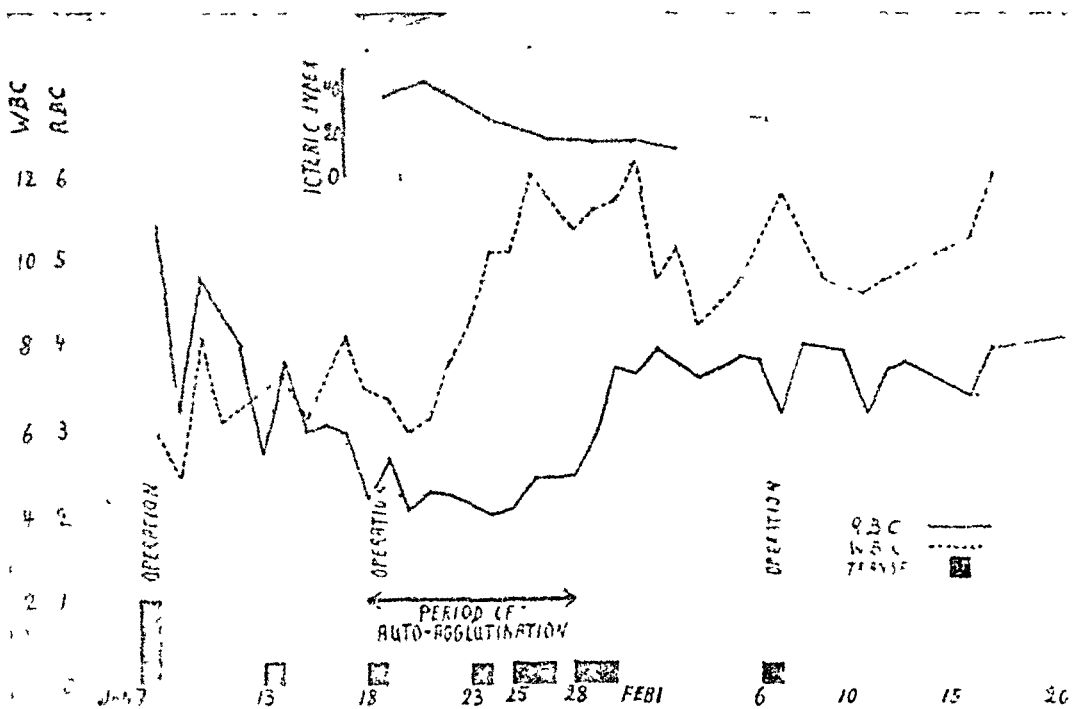


FIG. 1. The levels of the red blood cell and white blood cell counts following discontinuance of sulfonamide therapy on January 9. The period of auto-agglutination is indicated.

During the period of auto-agglutination (figure 1) repeated washing of the patient's cells with normal saline eliminated the agglutination, with other sera. This suggested that the agglutination, of the patient's unwashed cells with all sera, including "anti-B" rabbit antisera, was caused by the adsorption of agglutinins to the cell surface. Serial dilutions of the patient's serum set up with "O" cells at 4° C., as well as slide tests of patient's serum with type "A" and "O" cells, examined microscopically, failed to show definite evidence of "cold" isoagglutinins as described by Dameshek.<sup>2</sup>

#### SUMMARY

A case is presented showing hemolytic anemia, transient appearance of "cold" auto-agglutinins, and lack of leukocytic response to bacterial infection following administration of sulfonamides.

## BIBLIOGRAPHY

1. ANTOPOL, W., APPLEBAUM, I., and GOLDMAN, L.: Two cases of acute hemolytic anemia with auto-agglutination following sulfanilamide therapy, *Jr. Am. Med. Assoc.*, 1939, cxiii, 448.
2. DAMESHEK, W.: Cold hemagglutinins in acute hemolytic reactions in association with sulfonamide medication and infection, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 77.

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CALCIFICATION OF THE MYOCARDIUM \*

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IN 1924 Scholz<sup>1</sup> assembled from the literature 30 cases of calcification of the myocardium. He classified 14 as due to myocarditis. Oheim<sup>2</sup> has reported that minute deposits of calcium in the myocardium are not uncommon in fatal diphtheritic myocarditis. Scholz attributed three cases to coronary occlusion; five to sepsis and four to extension from calcification of the pericardium. He considered four the result of "calcium metastasis": Siebenmann's case of a man of 36 years with "extensive cystic degeneration of the long bones" and kidney stones, was thought by Siebenmann "one of plain calcium metastasis in the sense of Virchow, being secondary to the bone dissolving osteomalacic process." In the light of present day knowledge, this was obviously a case of hyperparathyroidism. A similar case was reported by Dawson and Struthers in 1923 (cited by Hanes<sup>3</sup>). Hanes in 1939 published the first instance of calcium deposits in the myocardium recognized by the author as the result of hyperparathyroidism.

In 1940 Brown and Evans<sup>4</sup> collected 14 cases of massive calcification of the myocardium. They, Redfearn,<sup>5</sup> Parkinson, Bedford and Thomson,<sup>6</sup> and Borman<sup>7</sup> have added four more original cases with autopsies. Massive calcification is usually the result of coronary occlusion.

Scholz made the first roentgenologic diagnosis of massive calcification. Parkinson, Bedford and Thomson have made the diagnosis in two cases (the second patient was still living at the time of their paper), and Borman<sup>7</sup> diagnosed his case in life. Roesler<sup>8</sup> discusses the diagnosis in his textbook and Sosman<sup>9</sup> in 1943 mentions seven cases. The diagnosis may have been made much oftener, but not a great many persons with such extensive infarction live long enough for calcification to be laid down.

The differential diagnosis involves chiefly calcification of the pericardium with perhaps extension into the myocardium, as reported by Clark.<sup>10</sup> It is important to make the distinction: if the calcification is limited to the pericardium and symptoms and signs of constriction are present, operative procedures may effect a cure.

Korinek<sup>11</sup> mentioned calcification of the coronary arteries and of the thoracic aorta in the differential diagnosis. He also added extension of calcification of the annulus fibrosus and presented exquisite plates of such a case. In his discussion, however, he considered that calcification of the myocardium sufficient to be picked up roentgenologically was usually a sequel of cardiac aneurysm. Apparently he had not personally encountered such a case.

\* Read before Fulton County Medical Society, February 7, 1946.

From Emory University School of Medicine, Department of Internal Medicine.

From the cardiac service of the General Hospital of Mexico City and the National Institute of Cardiology, Dorbecker<sup>12</sup> has reported seven cases of calcification of the mitral valve, three of the annulus fibrosus, six of the aortic valve and none of infarction.



FIG. 1. The left ventricle has been opened in the usual manner to expose the ballooning of the aneurysm and the thinness of the wall at the apex. The wire lies over the adherent pericardium. The background is divided into one centimeter squares.

#### CASE REPORT

In the spring of 1936, Mr. T., aged 59 years, considered himself in perfect health. Becoming concerned, however, over the sudden death of two friends, he secured additional life insurance. His blood pressure was 140 mm. of Hg systolic and 80 mm. diastolic.

On Saturday, May 2, and again on Sunday, Mr. T. played 27 holes of golf. Monday morning he awakened with a severe pain in the region of the xiphoid. The pain radiated through to the back, and had extended up under the shoulder blades by

the time the nearest doctor got there. This doctor found his blood pressure 174/94; he made a diagnosis of coronary thrombosis. On May 7 the retinal arteries were observed by me to be moderately sclerotic and the heart sounds very muffled. An electrocardiogram revealed an elevation of the S-T segment in Lead I with a depression in Lead III.



FIG. 2. Postmortem roentgenogram of the heart showing the calcification. The pericardium adherent to the apex may also be seen.

In September 1936 Mr. T. returned to work. He was not examined again until October, 1939. His blood pressure then was 164/120 and pulse 128. Fluoroscopic examination showed moderate enlargement of the heart with aneurysm of the left ventricle, and a tortuous, slightly dilated aorta. The electrocardiogram was diagnosed

as indicating an old infarction of the anterior wall with left bundle branch block. A year later his blood pressure was 130/114.

In the spring of 1945 Mr. T. began to experience from time to time pain across the upper sternum usually relieved by aspirin, and his activities were curtailed by undue tiring and breathlessness on exertion. On November 7 pain more severe than usual radiating up the sides of the neck caused him to call me. His blood pressure that morning was 134/100, the pulse 92. An electrocardiogram on November 8 showed no particular change from that in 1939.

November 16, in spite of paroxysmal cough and orthopnea, he came to my office. He weighed 118 pounds. Fluoroscopic examination, done hurriedly because of his breathless condition, showed further enlargement of the heart. Digitalis was prescribed, and frequent injections of salyrgan and aminophylline were started. On November 23, 700 c.c. of clear fluid were withdrawn from the left pleural cavity. Two weeks later Cheyne-Stokes respiration, noted for the first time, was promptly relieved by 0.5 gm. of aminophylline intravenously. The next day he had another severe attack, the periods of apnea lasting 30 seconds. He and his family refused to consider hospitalization. After that there were wide fluctuations in his general appearance: some days his color was good and he breathed comfortably; on others he was cyanotic, with respiratory distress and strutting of the veins of the neck. On January 9, 1946 he turned over unaided and died quietly.

*Autopsy:* The anterior surface of the left ventricle and the apex felt like bone. The pericardium was plastered against this part of the heart and there were also adhesions between the heart and the diaphragmatic surface of the pericardium. The heart was filled with clotted blood; the clots in the right ventricle were apparently post mortem, but those in the auricular appendages and over the infarcted area showed signs of organization. After removal of the clots the heart weighed 520 grams. The right coronary had been occluded recently about 1 cm. from its ostium. The anterior descending branch of the left coronary had been obliterated about 2 cm. below the bifurcation. Distal to this the heart was ballooned out and largely calcified. The infarcted area was roughly circular, 8 cm. in diameter; its inner surface was rough. It involved the apex, the anterior part of the left ventricle and the anterior centimeter of the interventricular septum. This area measured 0.3 to 0.4 cm. in thickness in contrast to an average thickness of 1.5 cm. for the remainder of the left ventricle. The valves were essentially normal. Rather severe grade of sclerosis was noted in the aorta. The right lung was crepitant throughout; there were many infarcts in the left lung with pleural effusion.

#### SUMMARY

A man 59 years of age experienced massive myocardial infarction on May 4, 1936. From September 1, 1936 to November 7, 1945 he was able to carry out his duties as vice president of a large concern, with apparently no cardiac symptoms until about nine years after the thrombosis. He died January 9, 1946.

Cardiac aneurysm was recognized fluoroscopically in 1939. It is believed that a more prolonged fluoroscopic examination on November 16, 1945, or an antemortem plate would have revealed the massive calcification of the myocardium.

As Scholz<sup>1</sup> said in 1924, "It may be worth noting that this apparent elimination of so large a portion of the heart muscle causes very little distress to the patient unless the conduction system of the heart happens to be interfered with by the calcifying process."

## BIBLIOGRAPHY

1. SCHOLZ, THOMAS: Calcification of the heart, its roentgenologic demonstration; review of the literature and theories of myocardial calcification, *Arch. Int. Med.*, 1924, xxxiv, 32-59.
2. OHEIM, LISLOTTE: Herzmuskelverkalkung bei Diphtherie, *Beitr. z. path. Anat. u. z. allg. Path.*, 1938, c, 222-228.
3. HANES, F. M.: Hyperparathyroidism due to parathyroid adenoma, with death from parathormone intoxication, *Am. Jr. Med. Sci.*, 1939, cxcvii, 85-90.
4. BROWN, C. E., and EVANS, W. D.: Primary, massive calcification of myocardium, *Am. Heart Jr.*, 1940, xix, 106-113.
5. REDFEARN, J. A.: Massive calcification of myocardium, *Am. Heart Jr.*, 1936, xii, 365-367.
6. PARKINSON, JOHN, BEDFORD, D. E., and THOMSON, W. A. R.: Cardiac aneurysm, *Quart. Jr. Med.*, 1938, vii, 455-478.
7. BORMAN, M. C.: Calcification of left ventricular infarction recognized during life, *Ann. Int. Med.*, 1943, xviii, 857.
8. ROESLER, HUGO: Clinical roentgenology of the cardiovascular system, 2nd edition, 1943, Charles C. Thomas, Publisher, Springfield, Ill.
9. SOSMAN, M. C.: The technique for locating and identifying pericardial and intracardiac calcification, *Am. Jr. Roentgenol.*, 1943, 1, 461.
10. CLARK, J. J.: Calcification of pericardium and within heart muscle, *Radiology*, 1940, xxxv, 356.
11. KORINEK, OTTO: Kardiovaskularni kalcifikace v roentgenove diagnostice, *Casop. lek. cesk.*, 1941, iccc, 491.
12. DORBECKER, N.: Las calcificaciones cardiacas y su significado, *Rev. med. y cien. afines*, Mexico, 1944, ii, 739-744.

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## COMPLETE HEART BLOCK IN CALCAREOUS AORTIC STENOSIS \*

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THE earliest recorded case of calcified stenosed aortic valve is that reported by Bonet in 1679 included in a series of case reports with autopsies; this was a post-mortem finding in a Parisian tailor who dropped dead in the street.<sup>1</sup>

Calcareous aortic stenosis has been the subject of considerable discussion for many years. As a result, it has become a well-recognized clinical entity which is, however, frequently undiagnosed because of the scarcity or absence of subjective symptoms. Objectively, there is often a dearth of physical signs, so that the condition becomes recognized only at postmortem examination. A fairly recent development is the demonstration of calcific masses in the aortic valve leaflets, annulus, or both, as seen by fluoroscopy.<sup>2</sup>

The etiology of calcareous aortic stenosis is still the subject of debate, although it is quite generally agreed that there is a distinct pathologic entity originally described by Mönckeberg. Christian<sup>4</sup> was convinced of the specificity of this condition. In addition, however, there are those cases in which calcification

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is superimposed upon the residuals of inflammatory valvular changes, such as occurs in rheumatic valvular disease and in healed cases of subacute bacterial endocarditis. It is usually agreed that syphilis is a rare precursor of calcification of a valve, if it ever is. Pure Mönckeberg's sclerosis occurs much less commonly than calcific aortic stenosis secondary to rheumatic fever. In a study of 40 cases by Karsner and Koletski<sup>5</sup> only three were believed to represent true Mönckeberg's sclerosis.

An interesting feature of calcareous aortic stenosis is the presence of complete heart block on rare occasions. The latter abnormality is usually listed as being caused by a variety of conditions. According to White,<sup>3</sup> "fibrosis of the bundle of His from coronary arteriosclerosis is the lesion most commonly found in heart block; infiltration by rheumatic, syphilitic or other infectious process, like bacterial endocarditis and calcareous extension from the region of the mitral or aortic valve which is calcified at its base, is occasionally encountered, while congenital defects of the bundle are rare."

Boas<sup>6</sup> stressed the occurrence of heart block in calcareous aortic stenosis. Cohen, Gray, Nash and Fink<sup>7</sup> in a report of nine cases of this disease cite the case of an 84 year old man whose heart at autopsy revealed fibrosis in the interventricular system probably due to an extension of calcific changes from the aortic valve and ring. They believed that this fibrosis in the interventricular system was responsible for auriculo-ventricular dissociation with complete heart block. Dry and Willius<sup>8</sup> made a study of 176 cases of calcareous aortic stenosis in which electrocardiographic records were available. Of these, 63 were examined at post mortem and in this group, there was one case with complete heart block in which the nodular excrescence of calcium extended from the mitral cusp of the aortic valve in such a manner as to involve the bundle of His. Of 85 cases showing marked calcareous aortic stenosis, two showed complete heart block. Reich<sup>9</sup> in a clinico-pathologic correlation of 22 cases of calcific aortic valve stenosis, reported one case with rheumatic etiology which presented both complete heart block and left bundle branch block.

#### CASE REPORT

A 52 year old negro male veteran of World War I whose occupation had been that of a laborer, was admitted to the hospital February 8, 1945, with history of onset of symptoms in May 1944, when he first noticed fatigue and discomfort in the anterior left chest and left arm brought on by exertion. This discomfort would last from 20 to 30 minutes at a time, and was usually relieved by rest. There was no nocturnal dyspnea. A private physician in August 1944 told him that he had high blood pressure; at that time he first noticed transient swelling of the feet and shortness of breath on exertion. About this same time he had suffered a convulsive seizure followed by hours of unconsciousness. The veteran was confined to bed by his physician until he was admitted to this Hospital.

*Past Medical History:* Penile sore at 16 years of age. Was given several injections of arsenicals and bismuth at a clinic near his home in Kentucky in 1944. No history of rheumatic fever or other rheumatic manifestations.

*Examination on Admission:* A chronically ill 50 year old negro male who was ambulatory. The cervical veins were somewhat distended but there was no cyanosis or edema. The lower lung fields posteriorly revealed scattered moist and musical râles. The pulse and cardiac impulse were synchronous, but irregular, their rate



being 50 per minute. A systolic thrill was palpated over the aortic area. The heart was markedly enlarged to the left, the apex being located by palpation and percussion in the sixth left interspace at the anterior axillary line. Systolic and diastolic murmurs were audible at the aortic area. The systolic murmur was rough, of great intensity, and heard loudest over the aortic area, although transmitted all over the precordium. The diastolic sound was blowing in character. A third heart sound was audible at the apical area. Blood pressure 190 mm. Hg. systolic and 110 diastolic. Peripheral vessels were sclerotic and tortuous. The abdomen revealed no hepatomegaly, splenomegaly or ascites.

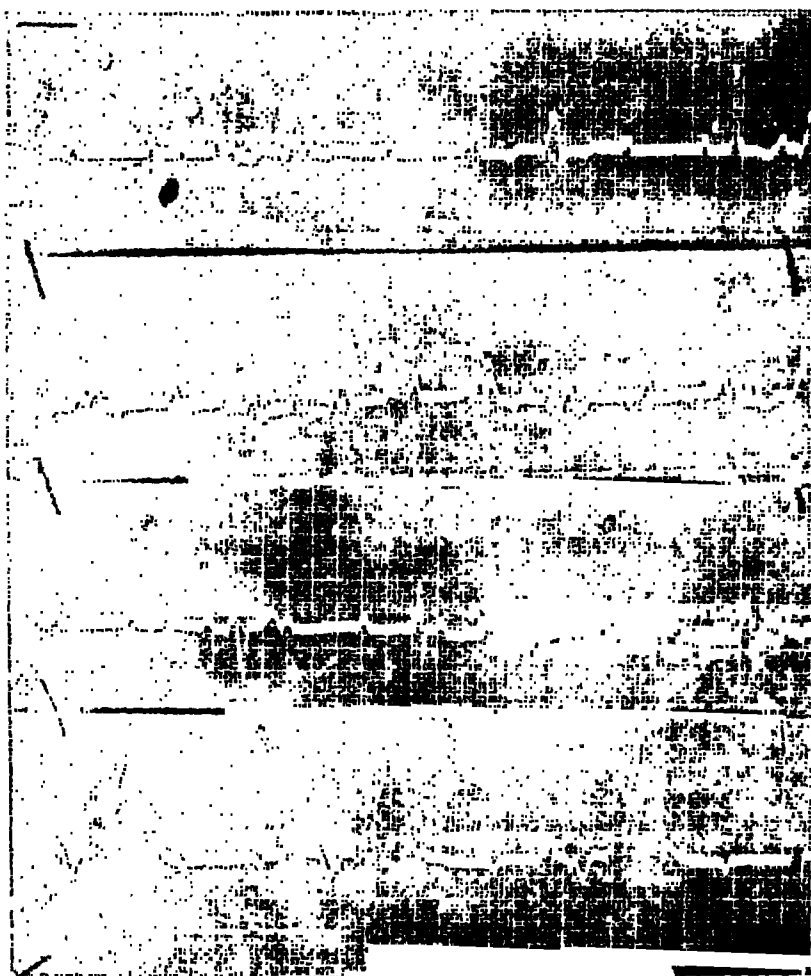


FIG. 1. Electrocardiogram showing complete heart block with auriculoventricular dissociation. Premature ventricular beats follow each normal ventricular complex.

*Laboratory Data:* Urinalysis: specific gravity 1.020; negative albumin and sugar; occasional white blood cells; no red blood cells or casts. Red blood cell count 5,020,000; hemoglobin 16 grams; white blood cells 7,300. Blood Wassermann test negative; Kahn 3; Kline 4. Blood non-protein nitrogen 35.7 and creatinine 1.5 mg. per cent.

Roentgen-ray of the chest revealed a mild degree of congestion in the hilar areas. The cardiac image was markedly enlarged, with a transverse diameter of 18 cm. as contrasted to a chest diameter of 29 cm. The aortic diameter was 6.5 cm.

Electrocardiogram on February 9, 1945, revealed complete heart block with A-V dissociation and many premature ventricular beats (figure 1). There was inversion

of  $T_1$ ; diphasic  $T_2$ ; upright  $T_3$  and inverted  $T_4$ . Left axis deviation was also present. Another electrocardiogram taken on February 10, 1945, was the same except for the absence of premature beats.

The combination of physical findings was somewhat confusing and a diagnosis of aortic stenosis and insufficiency was made. The etiology could not be established with certainty. The absence of a large pulse pressure and Corrigan pulse together with the distinct and pronounced aortic systolic thrill militated against a diagnosis of luetic aortic insufficiency. The most likely etiology was considered to be rheumatism.

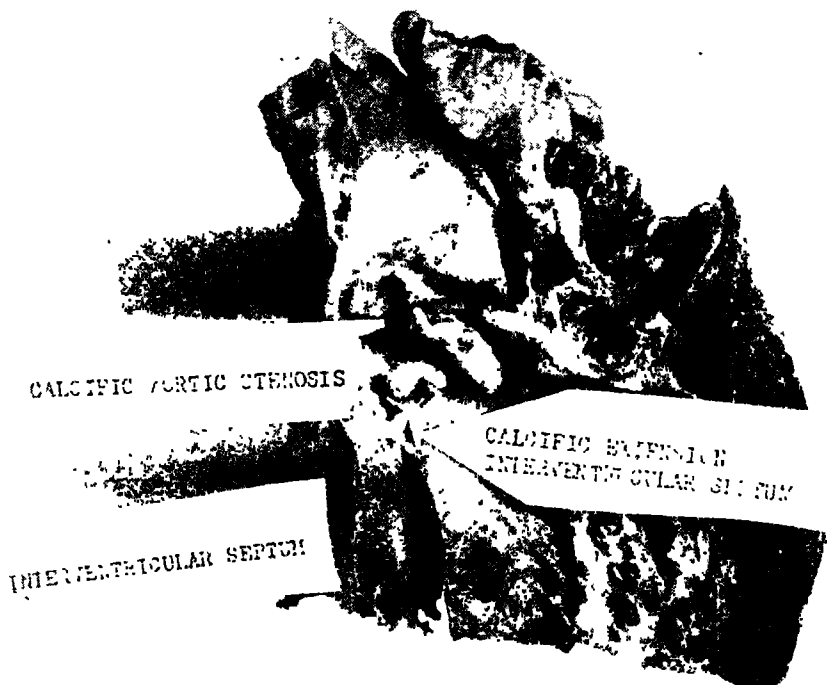


FIG. 2. Section of heart showing sclerosed aortic valve and calcific extension to the interventricular septum.

The heart block was attributed clinically to sclerosis involving the bundle of His or a gumma in the same area. The likelihood of impingement upon the membranous ventricular septum with disruption of the bundle of His by a calcific mass extending from a calcified aortic ring was also entertained. The pulse pressure of 80 mm. and the diastolic murmur at the aortic area were considered evidence against the classical calcific aortic stenosis.

*Course in the Hospital:* At no time was there abnormal elevation of temperature. No evidence of heart failure was ever noted on the ward. The patient spent most of his time in and near his bed; he had bathroom privileges. He complained frequently of vertigo and occasionally of substernal distress. On one occasion, he suffered an episode of unconsciousness from which he promptly recovered. This was considered to have been a Stokes-Adams attack. His pulse shortly afterward was 36 and blood pressure 218 mm. Hg systolic and 70 diastolic. During the first few weeks he was given 0.2 gram of bismuth subsalicylate intramuscularly twice weekly and saturated solution of potassium iodide; aminophylline by mouth was given continuously throughout the hospitalization. For a few weeks he had been given  $\frac{1}{400}$  grain of atropine sulfate subcutaneously three times daily. On August 3, 1945, he complained of

weakness while reading a paper; his pulse rate was 28 per minute. A few minutes later he died suddenly.

Excerpt from Post Mortem, August 6, 1945: Heart (Gross). The pericardial sac was essentially normal. The heart weighed 780 grams and showed considerable hypertrophy of the left ventricle. Several points of softening were noted in the left myocardium. The subepicardial fat was of normal amount and distribution. The auricles and auricular appendages were normal. The tricuspid valve was normal. The right ventricular chamber was slightly dilated; the musculature was soft. The left ventricle showed considerable hypertrophy of the muscle; the latter measured 2.2 cm. in thickness whereas the interventricular septum measured 2.5 cm.

The posterior leaf of the mitral valve was mainly involved. Here the *chordae tendineae* were thick and shrunken. The free edges were retracted. There was verrucous calcification at the base of the apron, continuous with the aortic involvement. The aortic valve was completely stenotic. The opening was irregularly triangular and elongated, measuring approximately 1.8 cm. at its widest point. There were extensive sclerotic and calcific changes and heaped up verrucous calcification on the ventricular side (figure 2). This verrucous involvement extended directly into the membranous portion of the interventricular septum. In the latter there was a small, nodular, calcific mass measuring approximately 3 mm. in diameter. The myocardium adjacent to this nodular calcification was slightly fibrotic, but otherwise showed no special features. The coronaries exhibited mild atherosclerosis. The ascending aorta showed atheromatous involvement. There was no evidence of luetic aortitis.

Histological examination of sections through the involved valves and myocardium revealed considerable sclerosis with thickening of the valve. At the base of the valve there was increased vascularity with a scattering of a few lymphocytes and monocytes. These showed no particular localization. In the interventricular myocardium adjacent to the nodular calcification considerable replacement fibrosis was present. In one area there was a suggestive Aschoff body. Sections of the remaining myocardium failed to reveal any evidence of similar rheumatic involvement, except for the presence of pseudonodular interstitial connective tissue in the perivascular regions. The conduction system was not visualized. The myocardial fibers exhibited myocardial degeneration consisting of fatty degeneration as well as interstitial fatty infiltration.

The pathology exhibited by this heart is consistent with old rheumatic valvulitis with subsequent fibrosis and calcification.

#### COMMENT

This case of calcareous aortic stenosis is believed to be of rheumatic etiology because of the co-existence of characteristic changes in the mitral valve leaflets. In addition, the presence of aortic insufficiency, too, would seem to be valid ground on which to make this assumption. True Mönckeberg's aortic sclerosis is not associated with clinical evidence of aortic insufficiency. The positive blood serology indicative of syphilis contributed to the confusion. Clinically the presence of the marked systolic thrill in association with a distinct aortic diastolic blow was strong evidence against luetic aortic insufficiency. At autopsy, no evidence of luetic aortitis was found and the coronary ostia were patent. This patient died suddenly, but we believe that his death was related to the complete heart block, rather than the aortic valvular lesion per se. Sudden death is not an uncommon occurrence in true calcareous aortic stenosis. We did not overlook the possibility that the complete heart block in this case could have been due to sclerosis in the septum, secondary to coronary arteriosclerosis. This is a very

common cause of heart block in older people. However, the location of the calcific mass extending from the aortic valve is such as to make it quite certain that this caused impingement on the neuromuscular tissue of the bundle of His.

### SUMMARY

A case of complete heart block is presented which occurred in an individual with rheumatic heart disease characterized clinically by aortic stenosis and insufficiency. The diagnosis of calcific aortic stenosis was entertained because of the characteristic thrill and murmur which usually occur in this condition. It was believed on clinical grounds that calcific extension to the bundle of His was the specific cause of the heart block. The postmortem findings substantiate this conclusion.

### BIBLIOGRAPHY

1. WHITE, P.: Heart disease, 1944, Macmillan Co., N. Y., Appendix I.
2. SOSMAN, M. C., and WOSIKA, P. H.: Calcification in aortic and mitral valves, with a report of 23 cases demonstrated in vivo by the roentgen-ray, *Am. Jr. Roentgenol.*, 1933, xxx, 328.
3. WHITE, P.: Heart disease, 1944, Macmillan Co., N. Y., p. 930.
4. CHRISTIAN, H. A.: Aortic stenosis with calcification of the cusps: a distinct clinical entity, *Jr. Am. Med. Assoc.*, 1931, xcvii, 158.
5. KARSNER, H. T., and KOLETSKI, S.: Calcific sclerosis of the aortic valves, *Trans. Assoc. Am. Phys.*, 1940, lv, 188.
6. BOAS, E. P.: Angina pectoris and heart block as symptoms of calcareous aortic stenosis, *Am. Jr. Med. Sci.*, 1935, cxc, 376.
7. COHEN, L., GRAY, I., NASH, P. I., and FINK, H.: Calcareous aortic stenosis. Report of nine cases with autopsy findings, *Ann. Int. Med.*, 1940, xiii, 2091.
8. DRY, T. J., and WILLIUS, F. A.: Interpretation of the electrocardiographic findings in calcareous stenosis of the aortic valves, *Ann. Int. Med.*, 1939, xiii, 143.
9. REICH, N. E.: Calcific aortic valve stenosis: A clinicopathologic correlation of 22 cases, *Ann. Int. Med.*, 1945, xxii, 234.

## EDITORIAL

### RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF GRANULOMA INGUINALE

GRANULOMA inguinale is a disease of probable venereal origin which holds little interest for the average practitioner, primarily because of the scarcity of such patients in private practice. However, those physicians who work in venereal disease clinics, particularly those below the Mason-Dixon line, find that the diagnosis and therapeutic management of this condition constitute a major problem.

Since the first adequate clinical description of granuloma inguinale by Conyers and Daniels<sup>1</sup> in 1896, many methods of diagnosis and many therapeutic procedures have been given trials with varying degrees of success. Donovan<sup>2</sup> first described the causative organism in 1905, and although he expressed the opinion that it was a protozoan he was unable properly to classify it. Following Donovan's discovery, several investigators claimed that they were able to culture the organism on different types of media, but these claims were not substantiated by reliable workers who tried the same technics. It was not until the work of Anderson, DeMonbreun and Goodpasture<sup>3</sup> that the Donovan body was successfully cultured and classified. These investigators used the yolk of chick embryos as a culture medium, and stated that the organism is a bacillus for which they proposed the name *Donovania granulomatis*. Kornblith<sup>4</sup> made an antigen by grinding a piece of tissue, heavily infected with Donovan bodies, in a mortar with a small amount of saline. After incubating the mixture at 60° C. for two hours on two successive days, and then testing it for sterility, he used it as an antigen by injecting 0.1 c.c. intradermally and observed the reactions in 24 hours. His claim that the antigen is specific is substantiated by the work of Anderson et al.<sup>5</sup> who carried out similar experiments, using a washed suspension of Donovan bodies which had been cultured in the yolk of chick embryos. These observations constitute an important contribution to the diagnosis of this disease. All investigators agree that clinical observation alone does not suffice, but that the presence of the organism must be demonstrated. In most clinics this is done by currettement of the margin of the lesion, staining a thick smear with Wright's or Giemsa stain, and searching for the characteristic intra- and extra-cellular bodies.

<sup>1</sup> CONYERS, J. H., and DANIELS, C. W.: The lupoid form of the so-called groin ulceration of this colony, *British Guiana Med. Ann.*, 1896, viii, 13-29.

<sup>2</sup> DONOVAN, C.: Ulcerating granuloma of the pudenda, *Indian Med. Gaz.*, 1905, xl, 414.

<sup>3</sup> ANDERSON, K., DEMONBREUN, W. A., and GOODPASTURE, E. W.: An etiologic consideration of *Donovania granulomatis* cultivated from granuloma inguinale (three cases) in embryonic yolk, *Jr. Exper. Med.*, 1945, lxxxix, 25.

<sup>4</sup> KORNBLITH, B. A.: The intradermal reaction as an aid in diagnosis of granuloma inguinale, *New York State Jr. Med.*, 1944, xlv, 2476.

<sup>5</sup> ANDERSON, K., GOODPASTURE, E. W., and DEMONBREUN, W. A.: Immunologic relationship of *Donovania granulomatis* to granuloma inguinale, *Jr. Exper. Med.*, 1945, lxxxix, 41.

An interesting sidelight is the fact that, although we can accurately diagnose this disease, we do not as yet know the mode of transmission and thus far the incubation period is still a mystery. Investigation of contacts has been fruitless, as the sexual partners of patients with extensive lesions have been proved to be clinically free of the disease. Two women with extensive involvement of the perineum were personally observed throughout their pregnancies in the Dermatology Clinic at the University Hospital in Baltimore. Both of these patients were delivered of normal living children who subsequently did not show any clinical evidence of granuloma inguinale. One theory of the mode of transmission is via an insect vector such as the *Pediculus pubis*. However, this theory seems untenable in view of the extreme rarity of pediculosis in the Negro, and the fact that the vast majority of these cases occur in colored people.

For many years following the original description it was assumed that granuloma inguinale was a local disease of the skin. It is a very destructive process and in some cases has been known to completely amputate the male genitalia as it progressed. Not until 1939, when Greenblatt and his co-workers<sup>6</sup> demonstrated the presence of Donovan bodies in lymph nodes, did it become apparent that the disease might cause systemic involvement. In 1944, Lyford, Scott, and Johnson<sup>7</sup> reported three cases of polyarticular arthritis and osteomyelitis due to granuloma inguinale. In the same year Pund and McInnes<sup>8</sup> reported six deaths due to the disease and from post-mortem findings concluded that the process may spread by way of the lymphatics or by surface continuity. From these reports we are forced to realize that we are dealing with a disease process which not only causes marked local destruction, but in some instances becomes generalized, and results in death.

Conyers and Daniels,<sup>1</sup> in their original report, advised surgical removal of the lesions. The first satisfactory chemotherapeutic measure was reported by Aragao and Vianna<sup>9</sup> in 1913. They advised intravenous administration of tartar emetic (antimony and potassium tartrate) in freshly prepared aqueous solution. Following this report, further investigations were made of the use of this drug by Pardo,<sup>10</sup> Low and Newham,<sup>11</sup> Randall, Small and Belk,<sup>12</sup> Johns and Gage,<sup>13</sup> Weinberg,<sup>14</sup> Hazen, et al.<sup>15</sup> Cole,<sup>16</sup> and

<sup>6</sup> GREENBLATT, R. B., DIENST, R. B., PUND, E. R., and TORPIN, R.: Experimental and clinical granuloma inguinale, Jr. Am. Med. Assoc., 1939, cxiii, 1109.

<sup>7</sup> LYFORD, JOHN, III, SCOTT, R. B., and JOHNSON, R. W., JR.: Polyarticular arthritis and osteomyelitis due to granuloma inguinale, Am. Jr. Syph., Gonorr. and Ven. Dis., 1944, xxviii, 588.

<sup>8</sup> PUND, E. R., and MCINNES, G. F.: Granuloma inguinale: a cause of death, Clinics, 1944, iii, 221.

<sup>9</sup> ARAGAO, H. DEB., and VIANNA, G.: Pesquisas sobre o granuloma venereo, Mem. do Inst. Oswaldo Cruz., 1913, v, 211.

<sup>10</sup> PARDO, V.: Ulcerating granuloma of the pudenda, Jr. Cut. Dis., 1918, iii, 206.

<sup>11</sup> LOW, G. C., and NEWHAM, H. B.: A case of ulcerating granuloma successfully treated by intravenous injections of antimony, Brit. Med. Jr., 1916, ii, 387.

<sup>12</sup> RANDALL, A., SMALL, J. C., and BELK, W. P.: Tropical inguinal granuloma in the Eastern United States, Jr. Urol., 1921, v, 539.

<sup>13</sup> JOHNS, F. M., and GAGE, I. M.: Granuloma inguinale and cultural studies of Donovan bodies, Internat. Clin., 1924, iv, 15.

Manson-Bahr.<sup>17</sup> All of these workers agreed that tartar emetic has curative value in the treatment of granuloma inguinale. Randall and his co-workers<sup>12</sup> stated that the results from the use of this drug in the treatment of granuloma inguinale were as striking as the results from the use of arsphenamine in syphilis. However, Cole<sup>16</sup> noted frequent relapses and Fraser<sup>18</sup> reported 62.5 per cent failures in his series of cases. In 1933 Williamson<sup>19</sup> investigated the use of another antimony compound, Fuadin, which he claimed to be more rapidly effective than tartar emetic and less reactive. In 1942 Robinson, Robinson, Jr., Mays and Shelley<sup>20</sup> reported a series of 62 cases. There were 39.2 per cent failures in those cases treated with antimony compounds. Excision of localized lesions was found to be an effective treatment in their hands, and this is still an acceptable therapeutic measure. Even after successful chemotherapy surgical intervention for the removal of scar tissue and the relief of lymphatic obstruction may be necessary. There is one general point of agreement in all the reports concerning the use of antimony compounds and that is expressed in the statement of Brandt and Gatewood,<sup>21</sup> "The effect of antimony compounds is pronounced in the early phases of the disease and decreases in direct ratio to its duration."

The advent of each new drug has acted as a stimulus to its trial in the treatment of granuloma inguinale. Ross<sup>22</sup> used sulfapyridine and claimed excellent results but no confirmation has been forthcoming. Nelson<sup>23</sup> and Haserick<sup>24</sup> proved that penicillin had no value in this disease.

The demonstration of the bacillary nature of the Donovan body by Anderson and her associates<sup>3</sup> led Barton, Craig, Schwemlein, and Bauer<sup>25</sup> to try streptomycin as a therapeutic measure. From this early report and others since there are indications that this drug surpasses antimony compounds in healing the lesions and that the percentage of relapses is much smaller.

The first study made by Barton and his associates was begun in February

<sup>14</sup> WEINBERG, M.: *Granuloma inguinale*, Jr. Urol., 1923, ix, 505.

<sup>15</sup> HAZEN, H. H., HOWARD, W. J., FREEMAN, C. W., and SCULL, R. H.: The treatment of granuloma in the negro, Jr. Am. Med. Assoc., 1932, xcix, 1410.

<sup>16</sup> COLE, H. N.: Venereal diseases with particular reference to granuloma inguinale and lymphogranuloma inguinale, Penn. Med. Jr., 1937, xl, 803.

<sup>17</sup> MANSON-BAHR, P. H.: *Ulcerating granuloma of the pudenda*. Manson's Tropical Diseases, 1940, Williams and Wilkins Co., Baltimore.

<sup>18</sup> FRASER, A. R.: *Granuloma inguinale*, Brit. Jr. Dermat., 1925, xxxvii, 14.

<sup>19</sup> WILLIAMSON, T. V., ANDERSON, J. W., KIMBROUGH, R., and DOBSON, A. L.: Specific effect of "Fuadin" (Fuadin) on granuloma inguinale: preliminary report, Jr. Am. Med. Assoc., 1933, c, 1671.

<sup>20</sup> ROBINSON, H. M., ROBINSON, H. M., JR., SHELLEY, H. S., and MAYS, H. B.: The treatment of granuloma inguinale, South. Med. Jr., 1942, xxxv, 889.

<sup>21</sup> BRANDT, R., and GATEWOOD, T. S.: Early diagnosis of granuloma inguinale, Am. Jr. Syph., Gonorr. and Ven. Dis., 1945, lii, 182.

<sup>22</sup> ROSS, A. O. F.: Granuloma inguinale treated with M & B 693, Lancet, 1939, i, 26.

<sup>23</sup> NELSON, R. A.: Penicillin in treatment of granuloma inguinale, Am. Jr. Syph., Gonorr. and Ven. Dis., 1944, xxviii, 611.

<sup>24</sup> HASERICK, J. R.: The failure of penicillin in the treatment of granuloma inguinale, Arch. Dermat. and Syph., 1945, lii, 182.

<sup>25</sup> BARTON, R. L., CRAIG, R. M., SCHWEMLEIN, G. X., and BAUER, T. J.: Granuloma inguinale treated with streptomycin, Arch. Dermat. and Syph., 1947, lvi, 1.

1946. They were able to demonstrate healing of the lesions in all of their cases before their limited supply of streptomycin was exhausted. One case was followed for two and a half months and no relapse was observed, but two of their cases developed new lesions because of inadequate dosage and the inability to continue treatment because the supply of drug had been exhausted. One noteworthy fact was established by this trial, however, and that was that the Donovan bodies disappeared from the lesions in from 10 to 20 days. In June 1947, Kupperman, Greenblatt and Dienst <sup>26</sup> reported on the results of their experiments with streptomycin in the treatment of granuloma inguinale. They treated 32 patients in whom they were able to establish the diagnosis of the disease by demonstrating the presence of Donovan bodies in stained smears from the lesions. In some of their cases the organisms disappeared from the lesions as early as the fourth or fifth day of treatment and all patients were free of the specific organisms at the end of 14 days. Their patients had almost immediate relief from pain following the institution of therapy. They noted recurrences in three cases, but none of these had received adequate dosage. There was complete involution of lesions in the remainder of the cases. This report was made at the American Medical Association Convention in June 1947. The discussion was opened by Dr. R. R. Kierland and Dr. Donald Pillsbury both of whom were enthusiastic about the results of this new form of therapy.

The reports to date therefore suggest that streptomycin will prove to be a specific for this debilitating and destructive disease process. If further experience proves this to be the case it is to be hoped that public funds will be forthcoming so that the new treatment may be made available to the indigent cases who comprise the majority of those afflicted with this disease.

H. M. ROBINSON, JR.

<sup>26</sup> KUPPERMAN, H. S., GREENBLATT, R. B., and DIENST, R. B.: Streptomycin in the therapy of granuloma inguinale. Presented at the Convention of the Am. Med. Assoc., June 12, 1947.



## REVIEWS

*Early Ambulation and Related Procedures in Surgical Management.* By DANIEL J. LEITHAUSER, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit, Michigan. 232 pages; 23 × 15 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1946. Price, \$4.50.

This is an excellent survey of the factors involved in early ambulation. Physiological principles of early ambulation are reviewed in a comprehensive and concise manner with clear differentiation of the terms "early ambulation" as opposed to "early rising."

The literature bearing on the subject is summarized and an excellent author reference listing is given.

Space is devoted to discussion of the physiopathological effects on the systems of the body of surgical procedures, and the accentuation of these effects by inactivity. The employment of various surgical technics and incisions is discussed in relationship to early ambulation. The importance of following physiologic principles in pre- and post-operative care, as well as at operation, is stressed.

The results in a remarkable series of 2047 cases are reviewed. In this series, there was no evidence of pulmonary embolism and only two cases of thrombophlebitis, the latter occurring early in the series. Wound disruption, which the author believes occurs on the fifth to ninth day postoperatively, is discussed in its relationship to early ambulation.

Detailed information is included regarding postoperative management, with an excellent description, well illustrated, of the technic of early ambulation.

This book is a valuable contribution to an important subject that requires constant emphasis. It could be improved by greater conciseness and elimination of extraneous material. Personal testimonials in a book of this character do not add to its intrinsic value.

G. H. Y.

*Pulmonary Tuberculosis: A Handbook for Students and Practitioners.* By R. Y. KEERS, M.D., M.R.C.P. (Edin.), F.R.F.P.S. (Glas.), Medical Director, Red Cross Sanatoria of Scotland, etc., and B. G. RIGDEN, M.R.C.S. (Eng.), L.R.C.P. (Lond.), First Assistant Medical Officer, Red Cross Sanatoria of Scotland, etc., with a Foreword by F. H. YOUNG, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H., Physician, Brompton Hospital for Consumption and Diseases of the Chest, etc. 227 pages; 19 × 12.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, \$5.00.

In this compact volume, the authors cover the entire disease in a simple, yet complete manner, so that it provides the answer to most questions relative to the disease. In general, the authors are in agreement with most of the present trends as accepted in this country.

Of particular note is the chapter "Examination of the Patient," in which the authors have deviated from the old pattern of emphasizing the physical examination. They have correctly given the roentgen examination a position second only to the history of the case, and have placed the physical examination as the least important of the diagnostic procedures.

The roentgenograms reproduced in the book are excellent, both from the standpoint of sharp delineation, and in the presentation of the various types of the disease and collapse therapy. These should prove to be of special interest to the reader.

The section devoted to collapse therapy is complete, and an evaluation of the various procedures is presented in a critical, but not confusing manner. A rather clear picture of the indications and contraindications of each method is offered.

The chapter dealing with "complications" is very good. Exception might be taken, however, to the author's rather radical policy as to therapeutic abortion in pregnant tuberculous women. In the major clinics in this country the indications for abortion under these circumstances are more restricted.

L. M. S.

*Microbial Antagonisms and Antibiotic Substances.* Revised Edition. By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers University; Microbiologist, New Jersey Agricultural Experiment Station. 415 pages; 16 × 24.5 cm. The Commonwealth Fund, 41 E. 57th St., New York, N. Y. 1947. Price, \$4.00.

Because of the rapid progress in knowledge of the formation, isolation and application of antibiotics, Dr. Waksman has revised the first edition of his well known work. Streptomycin and penicillin are adequately discussed, bringing the reader up to date with the findings of current research.

Dr. Waksman includes an exhaustive review of the literature dealing with the habitats, interrelationships and antagonisms among microorganisms. Bacteria, fungi, and animal forms acting as antagonists are discussed. Of significant practical value are the sections on the chemical nature of these substances and the various methods of measuring antibiotic action. Well written, sufficiently illustrated, this book serves as a basic text and is of inestimable value to the physician desiring information relative to the use of antibiotics as chemotherapeutic agents in the control of infection.

T. E. W.

*War Stress and Neurotic Illness.* Second Edition. By ABRAM KARDINER, M.D., with the collaboration of HERBERT SPIEGEL, M.D. 428 pages; 21.5 × 14.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1947. Price, \$4.50.

This book is written only for the psychiatric specialist, and more specifically for those working mainly with veteran or civilian traumatic neuroses.

The authors start by presenting an excellent discussion of the clinical pictures seen in both acute and chronic traumatic neuroses, and point out the true, but not too well accepted fact that a compensation factor hinders recovery. The main portion of the book is devoted to a theoretical evaluation and discussion of the data in an attempt to determine the nature of the traumatic neurosis. The authors approach this with a combination of reflexology and desexualized psychoanalysis: They arrive at the conclusion that traumatic neurosis is basically different from other psychiatric illness. There are no conclusions reached as to why some persons develop illness and others do not under similar circumstances, and no significant changes in therapy are recommended.

H. W. N.

## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Beiträge zur Kenntnis der Blutgerinnung.* By W. K. RIEBEN. 96 pages; 22.5 × 15.5 cm. (paper bound). 1947. Benno Schwabe & Company, Basel; imported by Grune & Stratton, Inc., New York. Price, 9 fr.

*The Clinical Examination of the Nervous System* (8th Edition). By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, etc. 380 pages; 19 × 13 cm. 1947. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$4.50.

*Cornell Conferences on Therapy* (Volume II). Edited by HARRY GOLD, M.D., Managing Editor, et al. 354 pages; 21 × 14 cm. 1947. The Macmillan Company, New York. Price, \$3.75.

*Dania Polyglotta.* Under the direction of K. SCHMIDT-PHISELDECK, with the collaboration of HENNING EINERSEN. 299 pages; 24.5 × 16.5 cm. (paper bound). 1947. Bibliothek Royale, Copenhagen. Price, 1 crown; Vol. 1901-1944, 3 crowns.

*Endocrinology (Experimental and Clinical): Being Section III of Excerpta Medica:* (A Complete Monthly Abstracting Service of the World Medical Literature Comprising 15 Sections and Covering the Whole Field of Theoretical and Clinical Medicine.) Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology, University of Amsterdam, etc. 64 pages; 25 × 16.5 cm. (paper). 1947. The Williams & Wilkins Company, Baltimore. Price, Subscription: \$15.00.

*Endogenous Endocrinotherapy*, including *The Causal Cure of Cancer: Compendium*, by DR. JULES SAMUELS, Specialist for endogenous endocrinotherapy, Amsterdam. 539 pages; 25 × 17.5 cm. 1947. Holdert & Company, Ltd., Amsterdam. Price, f. 24.

*Headache.* By LOUIS G. MOENCH, M.D., Assistant Clinical Professor of Medicine, University of Utah School of Medicine, etc. 207 pages; 21.5 × 14.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, \$3.50.

*Hodgkin's Disease and Allied Disorders.* By HENRY JACKSON, JR., A.B., M.D., Assistant Professor of Medicine, Harvard Medical School, etc., and FREDERIC PARKER, JR., A.B., M.D., Associate Professor of Pathology, Harvard Medical School, etc. 177 pages; 28.5 × 19.5 cm. 1947. Oxford University Press, New York. Price, \$6.50.

*A Neuro-Vascular Syndrome Related to Vitamin Deficiency.* By HENDRIK SMITS-KAMP. 114 pages; 24.5 × 15.5 cm. (paper bound). 1947. Scheltema & Holkema's Boekhandel en Uitgeversmaatschappij N.V., Amsterdam. Privately printed, no copies available.

*Physical Medicine in General Practice* (Second Edition, Revised and Enlarged). By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hospital, etc. With a chapter on Medical Rehabilitation by DR. SIDNEY LICHT. 686

pages;  $24.5 \times 16.5$  cm. 1947. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$8.00.

*Physiology of Man in the Desert.* By E. F. ADOLPH and Associates, Department of Physiology, University of Rochester. 357 pages;  $23.5 \times 16$  cm. 1947. Interscience Publishers, Inc., New York. Price, \$6.50.

*The Scientists Speak.* Edited by WARREN WEAVER. 369 pages;  $22 \times 14.5$  cm. 1947. Boni & Gaer, Inc., New York. Price, \$3.75.

*The Selected Writings of Benjamin Rush.* Edited by DAGOBERT D. RUNES. 433 pages;  $21 \times 14$  cm. 1947. The Philosophical Library, Inc., New York. Price, \$5.00.

*Spezifische Typhustherapie mit einem Beitrag zur Typhuspathogenese.* By DOZENT DR. FERDINAND NAGL and DR. OSKAR LACHNER. 63 pages;  $24 \times 17$  cm. (paper bound). 1947. Distributed in U. S. A. by Grune & Stratton, Inc., New York. Price, \$2.20.

# COLLEGE NEWS NOTES

## AMERICAN BOARD OF INTERNAL MEDICINE ANNOUNCES FORTHCOMING ORAL EXAMINATIONS

Oral examinations in the American Board of Internal Medicine will be conducted at San Francisco in April, 1948, and in Chicago in June, 1948, both periods immediately preceding the Annual Sessions of the American College of Physicians and the American Medical Association, respectively.

The closing date for registration for oral examinations is February 1, 1948.

The Board also announced the next written examination for October 18, 1948, with closing date for registration, June 1, 1948.

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## MEETING DATES

The 76th Annual Meeting of The American Public Health Association will take place at Boston, Mass., the week of November 8, 1948.

The Centenary Year Annual Session of The Medical Society of the State of Pennsylvania will occur October 4-7, 1948, at Philadelphia, Pa.

The 1948 annual meeting of the State Medical Society of Wisconsin will be held at Milwaukee, Wis., October 4-6, 1948.

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## LIFE INSURANCE MEDICAL RESEARCH FUND FELLOWSHIPS

The Life Insurance Medical Research Fund, 2 E. 103rd St., New York 29, N. Y., has announced that it will award about twelve fellowships for the year beginning July, 1948, to support laboratory and clinical investigation of cardiovascular problems. The annual stipend is stated to be between \$2,500.00 and \$3,500.00. Candidates must have an M.D. or Ph.D. or equivalent degree. The closing date for receipt of applications is January 15, 1948.

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The Faculty of the Medical School of the University of California announces the following postgraduate courses of interest to internists: Hematology and Blood Disorders, February 16 through 20, 1948; Internal Medicine and General Surgery, June 21 through 25, 1948.

Requests for detailed information should be addressed to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

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## 1948 NOMINATIONS, AMERICAN COLLEGE OF PHYSICIANS

At the 1948 Annual Business Meeting of the College at San Francisco, April 22, elections will be held for (a) Elective Offices, including President-Elect, First, Second and Third Vice Presidents; (b) Five members of the Board of Regents to fill vacancies of those whose terms expire in 1948; (c) Twenty members of the Board of Governors to fill vacancies of those whose terms expire in 1948.

Tenure of office of Regents is limited to two consecutive terms; of Governors,

to three consecutive terms. Thus some present incumbents are eligible for re-election, while others are not. The list of present incumbents is published elsewhere in this issue.

The By-Laws provide that the nominees for the Elective Offices of President-Elect, First, Second and Third Vice Presidents shall be published to the members of the College thirty days in advance of the Annual Business Meeting, but that nominees for the Board of Regents and Board of Governors may be announced directly at the Annual Business Meeting. It is, therefore, necessary that the nominees for the Elective Offices be selected in early January or February, 1948, but nominees for the Board of Regents and Board of Governors may be selected at greater leisure, but adequately in time for submission at the Business Meeting.

The Committee on Nominations, through its Chairman, Dr. William D. Stroud, 1011 Clinton St., Philadelphia 7, Pa., will gladly receive suggestions from FELLOWS and MASTERS concerning nominees for any of the posts to be filled, providing such suggestions are forwarded promptly after publication of this notice.

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#### CORRECTION—COMMITTEE CHAIRMEN SAN FRANCISCO ANNUAL SESSION

Correction is herein recorded of an error in the announcement of Committee Chairmen for the San Francisco Annual Session of The American College of Physicians, April 19-23, 1948, as published in the September, 1947, issue of this journal.

Hugh J. Morgan, M.D., President  
Vanderbilt University Hospital  
Nashville, Tenn.

(Program of Morning Lectures and  
Afternoon General Sessions)

William J. Kerr, M.D.  
University of California Hospital  
San Francisco 22, Calif.  
Ernest H. Falconer, M.D.  
384 Post Street  
San Francisco 8, Calif.

} Co-General Chairmen (Local Arrange-  
ments and Programs of Clinics and  
Panel Discussions)

Dwight L. Wilbur, M.D., Chairman, Committee on Clinics  
Sidney J. Shipman, M.D., Chairman, Committee on Entertainment  
George S. Johnson, M.D., Chairman, Committee on Hotels and Transportation

Roberto F. Escamilla, M.D., Chairman, Committee on Panel Discussions

William C. Voorsanger, M.D., Chairman, Committee on Publicity

Mrs. Stacy R. Mettier, Chairman, Committee on Ladies' Entertainment

Edward R. Loveland, Executive Secretary—General Manager of the Session  
4200 Pine Street  
Philadelphia 4, Pa. and Director of the Technical  
Exhibit

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#### A.C.P. COMMITTEE ON POSTGRADUATE COURSES INVITES SUGGESTIONS

The Advisory Committee on Postgraduate Courses of the American College of Physicians invites the members of the College to send into the Executive Offices of the College suggestions about postgraduate courses that are particularly desired. Not only would the Committee like to know the courses in which members are interested, but would gladly receive suggestions about the institutions at which such courses are desired and the directors under whom the courses might be organized.

It is desirable that the Committee be able to determine the number of members

who would support some particular course, because the College cannot afford to organize courses in which there would be inadequate registration.

A number of outstanding men at the Trudeau Sanatorium at Trudeau, N. Y., are willing to organize a course in pulmonary diseases. This undoubtedly would be one of the outstanding courses in this field in the country, and one that a reasonable number of members of the College would subscribe to. However, the Committee will appreciate it if members who would be interested in this course will so inform the Executive Offices of the College before such a course is scheduled. If there are an adequate number, the College will proceed in adding this course to its schedule.

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#### REPORTS ON RECENT REGIONAL MEETINGS

##### *Virginia A.C.P. Members Hold Interim Meeting*

About 50 members of the American College of Physicians from the State of Virginia held a dinner meeting at the Hotel Roanoke on October 14, in conjunction with the Annual Meeting of the Medical Society of Virginia. Dr. Charles M. Caravati, F.A.C.P., Richmond, was Chairman. Dr. Staige D. Blackford, F.A.C.P., Charlottesville, was elected Chairman for the coming year, and Dr. James Franklin Waddill, F.A.C.P., Norfolk, was re-elected Secretary. Dr. W. Halsey Barker, F.A.C.P., Baltimore, addressed the meeting and there were informal talks by Dr. Walter B. Martin, F.A.C.P., Regent of the College, Norfolk, and by Dr. J. Morrison Hutcheson, F.A.C.P., Richmond.

##### *Western Michigan*

A Regional Meeting for Western Michigan was held at the Muskegon Country Club, Muskegon, Mich., on October 29, 1947, under the Secretaryship of Dr. William M. LeFevre, F.A.C.P., Muskegon. The program consisted of the following papers: "Rocky Mountain Spotted Fever" by Dr. Gerald N. Rein, Benton Harbor; "Post-Menopausal Osteoporosis" by Dr. Silas C. Wiersma, Muskegon; "Silicosis in Industry" by Dr. Leland E. Holly, Muskegon. A reception and dinner were held in the evening, and Dr. Howard B. Carroll of Northwestern University delivered an address on "Duodenal Diverticula." The group voted to hold its next meeting at Battle Creek during the Spring of 1948.

##### *North Carolina*

On Friday, November 14, 1947, the Regional Meeting for North Carolina was held at Chapel Hill under the Governorship of Paul F. Whitaker, M.D., F.A.C.P., Kinston. Arrangements for the meeting were made by Robert L. McMillan, M.D., F.A.C.P., Winston-Salem, Chairman of the Program Committee, and Edward McG. Hedgpeth was Chairman of Local Arrangements. An afternoon session was held at the University of North Carolina School of Medicine, and the following papers were presented: "The Shoulder-Hand Syndrome," Elbert L. Persons, M.D., F.A.C.P., Durham; "Tropical and Parasitic Infestations in Veterans and Civilians in North Carolina," Thomas T. Mackie, M.D., F.A.C.P., Winston-Salem; "Clinico-Pathological Conference," Kenneth M. Brinkhous, M.D. (by invitation), Chapel Hill, and David Cayer, M.D. (Associate), Winston-Salem; "Effect of Lanatoside C on the Circulation of Patients with Congestive Failure: A Study Using the Technic of Right Heart Catheterization," Eugene A. Stead, Jr., M.D., F.A.C.P., Durham; and "Recent Advancement in the Treatment of Pulmonary Tuberculosis," H. Stuart Willis, M.D. (by invitation), Sanatorium. The evening session took place at the Carolina Inn and consisted of refreshments and an informal dinner with Dr. Whitaker acting as Toastmaster, and Dr. Mackie introducing the guest speaker, President Morgan.

*Tenth Annual Round-up of Eastern Pennsylvanians*

Dr. Edward L. Bortz, Governor for Eastern Pennsylvania and General Chairman of the Program, extended an invitation to members of the College and their guests in Pennsylvania, Southern New Jersey, and Delaware to attend this meeting held at the Warwick Hotel, Philadelphia, Friday, November 21, 1947. Burgess L. Gordon, M.D., F.A.C.P., and Henry F. Page, M.D., F.A.C.P., both of Philadelphia, presided over the afternoon session at which the following papers were presented by Philadelphia physicians. "Psychoanalysis," Kenneth E. Appel, M.D., Ph.D., Sc.D., F.A.C.P.; "Additional Homeostatic Mechanisms," Joseph T. Freeman, M.D. (Associate); "Atypical Pneumonia Simulating Tuberculosis," Daniel B. Pierson, Jr., M.D., F.A.C.P.; "Etiology and Treatment of Leukemia," Lowell A. Erf, M.D., F.A.C.P.; "The Rational Use of Physical Medicine in Geriatrics," Morris A. Bowie, M.D. (by invitation); "Significant Trends in Public Health," Pascal F. Lucchesi, M.D., M.P.H., F.A.C.P. Reception, cocktails, and informal banquet followed the scientific program. Dr. George Morris Piersol, M.A.C.P., was Toastmaster, and there were many distinguished guests, including President Hugh J. Morgan, Treasurer William D. Stroud, Executive Secretary Edward R. Loveland, the Deans and Presidents of Philadelphia medical institutions, and Governors of nearby territories.

*Southeastern Regional Meeting*

Alabama, Florida, Georgia, South Carolina, and Cuba joined, under the General Chairmanship of William C. Blake, M.D., F.A.C.P., Tampa, Fla., to present a two-day program at Tampa, December 8-9, 1947, with Dr. Blake, Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, and Dr. Robert Wilson, Jr., F.A.C.P., Governor for South Carolina, acting as Presiding Officers at the various sessions. The scientific program (Floridan Hotel, Monday morning and afternoon and Tuesday morning) consisted of the following: "Anticoagulant Therapy of Thromboembolic Disease," David F. James, M.D. (by invitation), Atlanta, Ga.; "Anticoagulant Therapy in Coronary Artery Disease," E. Sterling Nichol, M.D., F.A.C.P., Miami, Fla.; "Heart Rate and Circulatory Efficiency," Ashton Graybiel, M.D. (by invitation), Pensacola, Fla.; "The Treatment of Chronic Suppurative Disease of the Lung," Charles J. Donald, Jr., M.D. (by invitation), Birmingham, Ala.; "The Age Factor in Diabetes," George R. Wilkinson, M.D., F.A.C.P., Greenville, S. C.; discussion of the preceding papers opened by Glenville Giddings, M.D., F.A.C.P., Governor for Georgia, Atlanta, Ga.; "Epilepsy: Diagnosis and Treatment," Otto G. Wiedman, M.D., F.A.C.P., Hartford, Conn.; "Curable Forms of Heart Disease," A. Carlton Ernstene, M.D., F.A.C.P., Cleveland, Ohio; "Exophthalmos in Hyperthyroidism," Henry M. Thomas, Jr., M.D., F.A.C.P., Baltimore, Md.; "Clinical Considerations of the Problem of Extrarenal Excretion," Howard M. Odel, M.D., F.A.C.P., Rochester, Minn.; "Transfusion Reactions: A Neglected Medical Problem," John W. Williams, M.D., F.A.C.P., Bay Pines, Fla.; "Surgical Treatment of Hypertension," F. W. Cooper, M.D. (by invitation), Atlanta, Ga.; "The Purpuric State," Robert Wilson, Jr., M.D., F.A.C.P., Charleston, S. C.; "Diagnosis of Congenital Cardiac Anomalies," Harry T. Harper, Jr., M.D., F.A.C.P., Augusta, Ga.; discussion of preceding eight papers opened by Hugh J. Morgan, M.D., F.A.C.P.; "The Clinical Use of Rutin," Karl B. Hanson, MD., F.A.C.P., Jacksonville, Fla.; "Hyperventilation Syndrome," H. Phillip Hampton, M.D. (Associate), Tampa, Fla.; "Experimental Studies on Leukemia," William H. Riser, Jr., M.D. (by invitation), Birmingham, Ala.; "The Low Sodium Diet," Emil M. Isberg, M.D. (Associate), Miami Beach, Fla.; discussion of the preceding four papers opened by Turner Z. Cason, M.D., F.A.C.P. At the dinner Monday evening, Dr. Turner Z. Cason, F.A.C.P., Jacksonville, Governor for Florida, was Toastmaster, and the Guest Speakers were President Hugh J. Morgan, Nashville, Tenn., and Dr. James E. Paullin, Regent and Past President, Atlanta, Ga.



## DR. BURCH APPOINTED TO HEAD DEPARTMENT OF MEDICINE AT TULANE

George E. Burch, M.D., F.A.C.P., New Orleans, has been appointed to succeed the late John Herr Musser, M.D., M.A.C.P., as Professor of Medicine and Chairman of the Department of Medicine in the Tulane University of Louisiana School of Medicine. Dr. Burch received his M.D. Degree in 1933 from that institution, and in 1934 joined the staff of its Department of Medicine, in which he has most recently held appointment as Associate Professor of Clinical and Experimental Medicine. From 1939 to 1941 Dr. Burch was Assistant in the Rockefeller Institute for Medical Research, New York, N. Y., serving under Dr. A. E. Cohn. During the war he was appointed Consultant in Medicine (Cardiovascular) to the Surgeon General of the Army.

Dr. Burch is also Senior Visiting Physician to the Charity Hospital of Louisiana, and Visiting Physician to the Touro Infirmary, New Orleans.

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The Royal Australasian College of Physicians, with headquarters in Sydney, Australia, has conferred Honorary Fellowship on Dr. Hugh J. Morgan, President of the American College of Physicians, according to official notice received October 24, 1947, from Dr. S. A. Smith, President of the Royal College.

Dr. Morgan becomes the second Fellow of the American College of Physicians to be so honored, the first having been Dr. Noble Wiley Jones of Victoria, B. C. (formerly of Portland, Ore.), who was the official representative of The American College of Physicians at the inaugural ceremonies of The Royal Australasian College on December 14, 1938.

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Colonel Floyd V. Kilgore, (MC), USA, (Associate), Washington, D. C., has been awarded the Oak Leaf Cluster to the Legion of Merit for his distinguished service in initiating the Army's program for paraplegic cases in the Cushing General Hospital, December, 1944, to October, 1946.

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Colonel Arden Freer, (MC), U. S. Army, Retired, has been appointed Deputy Medical Director of the Veterans Administration.

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The Veterans Administration has announced the development of a center for research in cardiovascular disease at the Mount Alto Hospital, Washington, D. C. George P. Robb, M.D., F.A.C.P., Assistant Medical Director of the Metropolitan Life Insurance Company, New York, N. Y., has supervised the organization of this center and will continue to serve it as Consultant. In addition to research facilities, the center will provide consultative services and opportunities for graduate study and training.

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The National Gastroenterological Association, Inc., has rendered tribute to Hyman I. Goldstein, M.D. (Associate), Camden, N. J., by dedicating the Fifteenth Anniversary Number of its publication, THE REVIEW OF GASTROENTEROLOGY, to him on the occasion of his sixtieth birthday.

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The first annual meeting of the California Society of Internal Medicine, which has a membership of more than 400 internists, was held recently in Los Angeles. Members of the College who have been elected officers of the Society are Donald E. Griggs, M.D., F.A.C.P., Los Angeles, President; Harold C. Torbert, M.D., F.A.C.P.,

San Diego; C. Kelly Canelo, M.D., F.A.C.P., San Jose; Frank B. Reardan, M.D. (Associate), Sacramento; and Gurth Carpenter, M.D. (Associate), Beverly Hills; Councilors.

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Finland has an excellent Technical Institute, Teknillinen Korkeakoulu. During the war its library was bombed and totally destroyed.

Martti Levon, Director of the Institute, states that in the remarkable efforts for recovery that the Finns are making, the lack of technical library facilities is a very serious handicap.

It would be a practical act of friendship to a nation that holds America in high regard if Americans should contribute good technical books and periodicals to this library. Any such gifts should be marked for the Institute of Technology, Helsinki, and sent to the Legation of Finland, 2144 Wyoming Ave., N.W., Washington, D. C. Dr. K. T. Jutila, the Finnish Minister, will arrange for their being shipped to Finland.



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JOHN HERR MUSSER, B.S., M.D., M.A.C.P.

## OBITUARIES

JOHN HERR MUSSER, B.S., M.D., M.A.C.P.

## MEMOIR

When Dr. John Herr Musser, a Master of this College, died on September 5, 1947, at his home in New Orleans, American medicine lost a great internist, the American College of Physicians an ardent supporter, and a long succession of able doctors came to an end.

John Musser, born in Philadelphia on June 9, 1883, came of sturdy Lancaster County stock and was the sixth member of his family in direct descent to become a physician. With such a background and with a father who was one of the outstanding internists of his day and Professor of Clinical Medicine at the University of Pennsylvania for many years, it was not surprising that even during his school days the younger Musser was bent upon following the family tradition. His later achievements as a physician and teacher amply justified the wisdom of his choice of medicine as a career.

Dr. Musser, after attending the famous old William Penn Charter School in Philadelphia, received his Bachelor of Science degree from the University of Pennsylvania in 1905, and his Doctor of Medicine degree from the same institution in 1908. After two years of internship and a course of graduate study at the University of Amsterdam, Dr. Musser entered upon the practice of Internal Medicine in Philadelphia with his father, an association which terminated with the death of Dr. Musser senior in 1912. Young Musser's skill as a physician and ability as a teacher were soon apparent. In 1912 he became visiting physician to the Presbyterian Hospital of Philadelphia, and in 1914 was given a similar title on the staff of the Philadelphia General Hospital. His teaching career began with his appointment in 1914 as Associate in Medicine on the faculty of the School of Medicine of the University of Pennsylvania. A few years later he was made an Assistant Professor of Medicine and in 1920 was promoted to Associate Professor of Medicine in the same medical school.

With the entry of the United States into World War I, Dr. Musser was among the first physicians to renounce a successful practice and give up active teaching to enter the Medical Corps of the United States Army with the rank of first Lieutenant. As a medical officer he proved as popular and as successful as he was as a civilian physician. In 1918 he was sent to France as a member of the University of Pennsylvania's Base Hospital No. 20. While with that organization he earned his majority and became Chief of the Medical Service. Upon his discharge from the Army in 1919, unlike most of his colleagues, he never lost interest in the Medical Department of the Army. He reentered the Medical Reserve Corps, attaining the rank of Colonel in that organization in 1938. During World War II, he was appointed by the Secretary of War a member of a committee to study the reorganization of the Surgeon General's Office.

Upon the completion of his active duty with the Army in 1919, Dr. Musser returned to Philadelphia to take up his consulting and hospital practice in Internal Medicine and assume more exacting teaching obligations. At this time he took over the added duties of physician to the Howard Hospital of Philadelphia. It required but a few years to convince Dr. Musser that the ever increasing demands and responsibilities of a growing practice left too little time for the pursuit of the more academic and literary medical activities wherein had always lain his greatest interest. A welcome

solution of his problem came when, in 1924, he was appointed Professor of Medicine and Head of the Department of Medicine at Tulane University School of Medicine in New Orleans, a position which he filled with distinction until his death.

The past twenty odd years that Dr. Musser spent in New Orleans represent the most scientifically profitable and productive period of his life. As the first full-time Professor of a clinical department in the medical school at Tulane, he was able to devote successfully his time and energies to teaching, writing and investigation from which he derived much satisfaction and happiness.

Dr. Musser's activities and interests were many and varied. He was known not only as a clinician and medical teacher of unusual distinction but also for his work in the field of Public Health. He served as Director of the Louisiana State Board of Health from 1940 to 1942, during which time he completely reorganized the public health administration machinery of the State for which he was acclaimed by Governor Jones of Louisiana. He served as President of the New Orleans Tuberculosis Association for fourteen years as well as being a Director of the Child Guidance Center and President of the New Orleans Institution for Mental Hygiene.

Regardless of his other interests Dr. Musser was always engaged in literary activity. From 1922 to 1925, he was Editor of the American Journal of the Medical Sciences, having been Assistant Editor for a number of years previously. At the time of his death he was Editor of the New Orleans Medical and Surgical Journal, a responsibility which he assumed in 1927, as well as being a member of the Editorial Board of the Archives of Internal Medicine. He edited and contributed to the important text book "Internal Medicine," which is widely known by his name. The fourth edition appeared in 1945 and the fifth was already in preparation at the time of his death. He revised and edited through four editions the well known textbook on physical diagnosis written by his father, in addition to rewriting two other medical texts. During his life his contributions to contemporary medical journals and presentations before medical societies amounted to well over 100.

Even to the last days of his life his interest in organized medicine never waned, as was evident from his many activities in connection with county and state societies and the American Medical Association. He held many positions in the latter organization. From 1934 on, he was a member of the Council on Medical Education and Hospitals of the American Medical Association. In 1933 to 1934, he was Vice-President and later Chairman of the Section on Pharmacology and Therapeutics of the American Medical Association. From 1937 to 1938, he served as Chairman of the Section on the Practice of Medicine and in 1928 he was a member of the House of Delegates of the American Medical Association.

Dr. Musser was a member of many scientific societies of national importance, notably the Association of American Physicians, American Society of Clinical Investigation, Association for Research in Nervous and Mental Diseases, American Clinical and Climatological Association, College of Physicians of Philadelphia, the Society of Internal Medicine of the Asociación Médica Argentina, Buenos Aires, of which he was a foreign corresponding member, and the American College of Physicians. It was to the last organization that he gave his greatest allegiance and for which he entertained a deep affection. Elected a Fellow in 1920, Dr. Musser served on the Board of Regents from 1926 to 1936, and was President of the College from 1929 to 1930. In these capacities he played a leading rôle in the reorganization of the College, its expansion and development. Throughout his long association with the College he proved himself an indefatigable worker on many committees, including some years of service on the Credentials Committee. In recognition of his years of unselfish devotion, the College bestowed upon him, in 1947, its greatest honor, a Mastership. No group feels more keenly the loss of Dr. Musser than do his loyal friends of the American College of Physicians, especially those who, privileged to work

closely with him on many occasions, came to depend upon his wisdom and good judgment.

Of the many honors that were bestowed on Dr. Musser there were none that brought him greater satisfaction than his election a few years ago as an Alumni Representative to the Board of Trustees of his alma mater and the Alumni Award of Merit of the University of Pennsylvania School of Medicine which he received in 1940. Dr. Musser was not only a diplomate of the American Board of Internal Medicine, but for a number of years served as a member of that certifying body.

It was not so much Dr. Musser's lasting contributions to American medicine and to medical education in this country that so endeared him to all with whom he came in contact as his remarkable personality and charm. His irresistible sense of humor and unfailing cheerfulness were tempered with poise and equanimity. The patience, tolerance and unselfishness characteristic of a great gentleman marked his every act. Yet, with all, he possessed dogged determination and a fearlessness of spirit that enabled him to meet all serious issues with uncompromising honesty. The last years of his full and useful life were marred by serious illness, the disastrous results of which he fully appreciated. In spite of irksome disability and discomfort he never lost interest in his work and to the very last day of his life faced each problem with uncomplaining courage.

His widow, the former Marguerite Hopkinson, his daughter, Mrs. Thomas L. Avengo, four grandchildren, and his sister, Mrs. Richard M. Pearce, are the only surviving members of his immediate family. To them this College extends sincere and heartfelt sympathy. Their loss, irreparable as it is, is not theirs alone; it is shared by all whose good fortune it has been to count as a friend John Musser, teacher, author, investigator, and above all a great understanding physician.

GEORGE MORRIS PIERSOL, M.D., M.A.C.P.,  
Secretary-General, ACP

#### DR. LAURENCE COLEMAN MILSTEAD

Laurence Coleman Milstead, M.D., F.A.C.P., formerly of Allentown, Pa., died August 31, 1947.

Dr. Milstead was born in Washington, D. C., on September 5, 1899. His collegiate and medical studies were carried out in Georgetown University from which he obtained the degree of Doctor of Medicine in 1924. He served as intern in the Georgetown University Hospital, and then held positions for over three years as assistant clinical pathologist in various Washington hospitals. He was appointed clinical pathologist in the Sacred Heart Hospital, Allentown, Pa., and held this position until 1940. During this time he obtained the respect of local physicians for the thorough knowledge and method of his many presentations of clinical material.

In 1940 Dr. Milstead opened a private laboratory and engaged in consultative work, but left this behind to enter the Army as a Major in 1942. His military record, which continued until June of 1947, included service with the 220th General Hospital in France. Resuming civilian life, Dr. Milstead became pathologist to the St. Mary's and Blessing Hospitals, Quincy, Ill., shortly before his death.

A diplomate of the American Board of Pathology, Dr. Milstead was a member of numerous medical organizations, and was active in their proceedings. He became a Fellow of the American College of Physicians in 1936.

WILLARD D. KLINE, M.D., F.A.C.P.

## COLONEL ROBERT D. HARDEN, M.C., USA

Colonel Robert DuRant Harden, Medical Corps, USA, Retired, F.A.C.P., died August 6, 1947, at Pratt General Hospital, Coral Gables, Fla., where he had been taken from his home in Marathon, Fla.

Born in 1888 in Commerce, Ga., and graduated from Atlanta College of Physicians and Surgeons in 1911, Dr. Harden was commissioned a First Lieutenant, Medical Corps, Regular Army, May, 1915, after fifteen months' service in the Medical Reserve Corps. He served in France, 1918; at Letterman General Hospital, San Francisco, California; as Assistant Corps Area Surgeon of First Corps Area; and three different times in the Office of the Surgeon General, Washington, D. C., receiving a letter of commendation from the Surgeon General for services as Assistant and Chief of the Finance and Supply Division.

In 1928 Dr. Harden was awarded the degree of Master of Public Health by Harvard University. Because of his interest in public health work he was made Assistant Superintendent and Superintendent of Gorgas Hospital, Panama, and received the Legion of Merit award for these three years of service. Colonel Harden was chosen Commanding Officer of Crile General Hospital, Cleveland, Ohio, upon its establishment. Under his guidance this installation increased its bed capacity, maintained high standards of medical care, and developed a most cordial relationship with the City of Cleveland. For unselfish devotion to this duty he was awarded the Oak Leaf Cluster to the Legion of Merit, March, 1946. He retired March 31, 1946.

Colonel Harden was a Fellow of the American College of Surgeons, and of the American Public Health Association. He was elected a Fellow of the American College of Physicians in 1929.

## DR. H. CLIFF SAULS

H. Cliff Sauls, M.D., F.A.C.P., of Atlanta, Ga., died on July 15, 1947. Dr. Sauls was born in Cobb County, Ga., on February 28, 1887. He was graduated in 1913 from the Medical Department of Emory University, which was then known as the Atlanta College of Physicians and Surgeons. He served in World War I as a Captain in the Medical Corps, being a member of the first Emory Unit. He was Associate Professor of Medicine at Emory University and served on the staffs of the Piedmont and Grady Memorial Hospitals in Atlanta, and the Scottish Rite Hospital for Crippled Children in Decatur. He was a member of the Fulton County and Georgia State Societies and of the Southern Medical Association; and a Fellow of the American Medical Association. Dr. Sauls was elected to Fellowship in the American College of Physicians in 1928 and was a diplomate of the American Board of Internal Medicine.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,  
Governor for Georgia

# ANNALS OF INTERNAL MEDICINE

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